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American Heart Journal

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Original Communications

THE DISTRIBUTION OF POTENTIAL OF VENTRICULAR ORIGIN BELOW THE DIAPHRAGM AND IN THE ESOPHAGUS

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RECENT studies of Wolferth, Livezey, and Wood,[1, 2] using methods by which the potential transmitted to an exploring electrode can be reflected in electrocardiograms with minimal distortion, have shown that a pattern of potential variation which they called the diaphragmatic pattern is widely distributed over the surface of the human body below the level of the diaphragm. A few observations made with an exploring electrode in the stomach and in the esophagus below the auricular level indicated that the diaphragmatic pattern tends to be distributed to these areas, also. Limited animal experiments in the dog and rat, in which the exploring electrode was paired with one inserted in the right foreleg, likewise indicated that one pattern of potential is distributed to the legs, the surface of the trunk below the diaphragm, and the abdominal cavity, including the undersurface of the diaphragm except the part very near the heart.

In connection with a study by Forster, Helm, and Ingelfinger[3] on action potentials of the gastrointestinal musculature, it was decided to make further observations on the comparison of ventricular patterns of potential variation developed on the left leg with those of the front and back of the trunk below the level of the umbilicus,* the small

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*The studies of Wolferth, Livezey, and Wood[2] have indicated that the patterns of potential variation recorded at various positions on the body surface between the levels of the parietal attachments of the diaphragm and the umbilicus are composites made up of the diaphragmatic pattern, and patterns better recorded above the diaphragm. The decrement in the latter is so rapid below the diaphragm that they usually exert a negligible influence on potential patterns below the level of the umbilicus. These composite effects, however, between the levels of the diaphragm and the umbilicus, make this zone of dubious value for the study of ventricular potential. For this reason it was not included in the present study.

intestine, duodenum, stomach, and esophagus. Such observations, it seemed to us, should yield information regarding the distribution of the diaphragmatic pattern of potential and also throw some light on the usefulness of inserting electrodes into the gastrointestinal tract for study of the cardiac action currents.

MATERIAL AND METHODS

The subjects were patients from the Gastrointestinal Clinic and the Medical and Surgical Wards of the Massachusetts Memorial Hospital. Electrocardiograms were made with a Sanborn tri-beam galvanometer. In the experiments in which the exploring electrode was placed in the gastrointestinal tract, three types of electrodes were used: (1) a solder disc electrode 4 mm. in diameter on a tube described previously,[3] (2) a standard Rehfuss tip 9 by 17 mm., or (3) a small metal tip 5 by 7 mm. The tips were soldered to No. 32 enameled copper wire, conducted through rubber tubing so that insulation was complete except for the tip. The tubes were passed either orally or through the nose, and were manipulated into the desired position under fluoroscopic guidance. With the exception of four cases mentioned, the exploring electrode was paired with one placed over the spine of the right scapula, an area shown by the method of balanced potentials to be one of relatively slight cardiac potential variation.[2]

COMPARISON OF VENTRICULAR PATTERNS OBTAINED WITH THE EXPLORING ELECTRODE ON THE LEFT LEG AND VARIOUS OTHER POSITIONS

Anterior Abdominal Wall.—The pattern of potential variation found with an exploring electrode on the anterior abdominal surface midway between the umbilicus and the symphysis was compared with the left leg pattern in 18 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In 14 cases the patterns were practically identical in every respect, including amplitude of deflections. In three cases the patterns were practically the same qualitatively, but the amplitude of deflections recorded from the abdominal wall was slightly smaller than that recorded on the left leg. In one case the patterns differed slightly in that an S deflection (new nomenclature) extended a little further below the isoelectric line in the abdominal pattern.

Posterior Abdominal Wall.—The potential patterns recorded with an exploring electrode on the midline of the back below the umbilical level were compared with the potential patterns of the left leg in the same 18 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In all cases the patterns were similar qualitatively, but in only two were the deflections of approximately the same size. In the other 16 cases the deflections were smaller when the exploring electrode was placed over the back than when it was placed on the leg.

Small Intestine.—A comparison of the potential variations of the interior of the small intestine beyond the duodenum with those of the left leg was made in four cases (Fig. 2, *A*, *B*, and *C*). In these cases, the exploring electrode, which was passed beyond the ligament of

Treitz, was paired with an electrode on the right arm, and this lead compared with Lead II. In each of the four cases the two leads were practically identical. In two of the cases in which the electrode in the intestine was paired with one on the left leg, only a negligible difference of potential was recorded.

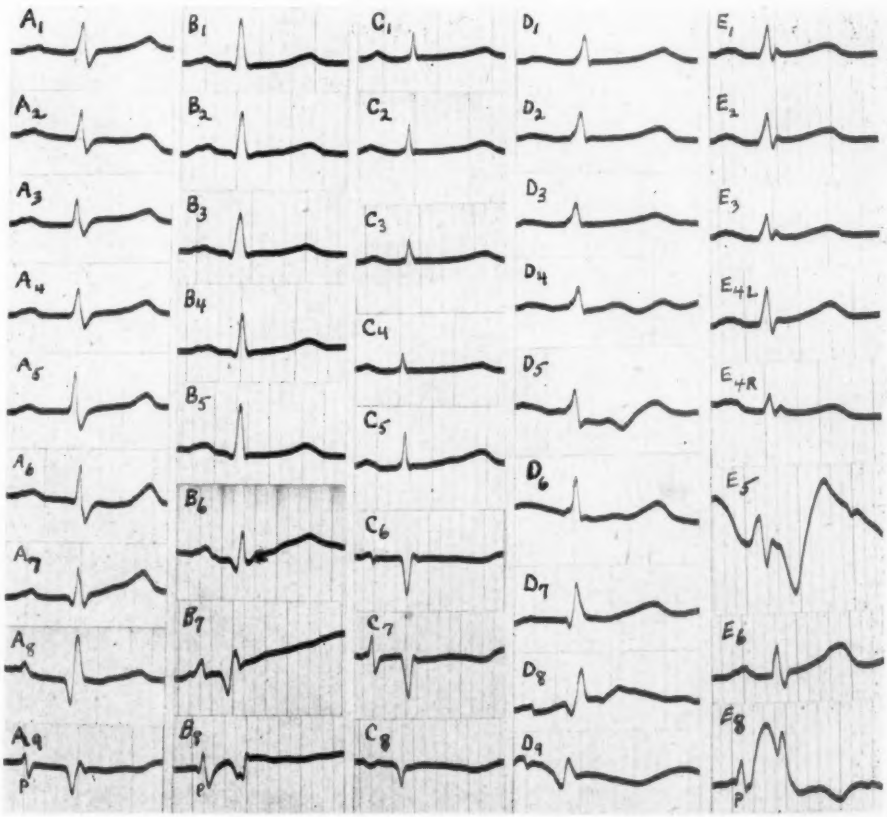

Fig. 1.—The letters *A*, *B*, *C*, *D*, and *E* designate cases, and the numerical subscripts, the positions of the exploring electrode. Thus, *1* designates the left leg; *2*, the anterior abdominal wall below the umbilicus; *3*, the mid-back at the same level as *2*; *4*, the duodenum (½ *R* the right side and ½ *L* the left side); *5*, the stomach; *6*, just within the lower end of the esophagus; *7*, approximately 1 to 1½ inches higher in the esophagus; *8*, at the mid-cardiac level; and *9*, the level of the top of the heart.

In *A* note the similarity of pattern with the exploring electrode at various positions from the left leg to the lower end of the esophagus, and then, as the electrode is moved to positions higher in the esophagus, the gradual development of a large Q deflection and inversion of the T wave (the "endocardial pattern"). In *B* the similarity of pattern is preserved as near the heart as the stomach. At the lower end of the esophagus, the beginning change to the endocardial pattern is reflected by an increase in amplitude of the Q wave. In *C* the pattern is also preserved as near to the heart as the stomach, but at the lower end of the esophagus the pattern is already of the endocardial type. In *D*, a case in which there was marked enlargement of the liver and spleen, the QRS complex pattern is preserved as high as the lower end of the esophagus, but there is RS-T segment deflection in the duodenal, stomach, and lower esophageal leads; this is, in all probability, an artifact caused by movement of the electrode. In *E* the correspondence between the QRS complex of the lead with the exploring electrode on the leg and the two leads made with the exploring electrode in different parts of the duodenum is the poorest obtained between leg and duodenal leads. In the lead made with the exploring electrode in the stomach (E_5), note the marked distortion following the QRS complex, and, in the esophageal lead (E_8), the marked distortion following auricular activation. These effects, like those pointed out in *D*, are regarded as artifacts produced by movement of the electrode. They recur regularly with every beat.

Duodenum.—The potential patterns recorded with an exploring electrode in the descending portion of the duodenum were compared with those of the left leg in 24 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In 14 cases the patterns were practically identical. In 5 cases the patterns were the same except that the deflections in the duodenal lead were uniformly smaller (Fig. 1, *C*). In one case the patterns were the same except that the deflections in the duodenal lead were uniformly larger. Of the other four cases, three showed minor differences in the QRS complex from that of the corresponding leg lead, and two showed differences in T waves. In one of these four cases in which leads were made from both the descending and distal portions of the duodenum, leads from neither portion showed accurate correspondence with the leg lead with respect to the S deflection (Fig. 1, *E*). Inspection of these tracings, however, suggested that the mean potential of the two duodenal areas would have resembled the leg pattern of potential variation fairly closely.

Stomach.—The patterns of potential variation of the left leg were compared with those of one or two parts of the stomach in 36 cases.

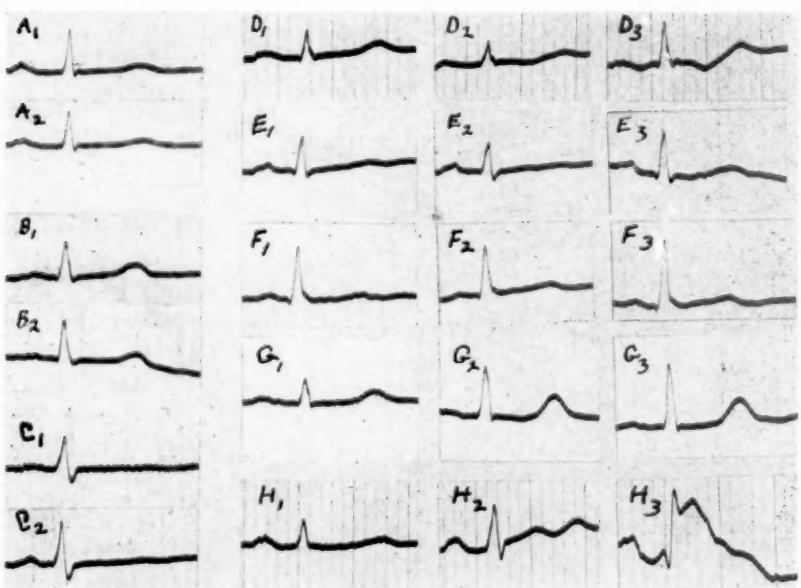

Fig. 2.—In *A*, *B*, and *C* the upper complex of each pair is Lead II; in the lower complex the right arm electrode remained on the right arm, but the left leg lead wire was connected with an electrode in the jejunum. Note the close correspondence of patterns in each pair.

In *D*, *E*, *F*, and *G* the subscript *1* designates a lead with the exploring electrode on the left leg, paired with an electrode over the spine of the right scapula. The subscript *2* designates that the exploring electrode was in the right side of the stomach, and *3*, that it was in the left side of the stomach. Note that the deflections were larger when the exploring electrode was in the left side of the stomach. In *D* and *E* minor differences of patterns are found in the QRS complex, but in *F* and *G* there is close correspondence of the entire ventricular patterns except for the amplitude of deflections.

In H_1 the exploring electrode was on the left leg in H_2 in the stomach and, in H_3, in the lower end of the esophagus. Note the marked RS-T segment deflection in the esophageal lead, which is almost certainly an artifact produced by movement of the electrode during the heartbeat. The diphasic T wave in D_2 and D_3 was probably caused by the same phenomenon.

We wish first to present the data in 12 cases in which the tracings were made with the exploring electrode in the pyloric region, and then on the left side in the fundus as near the left side of the diaphragm as possible. In six of these cases the potential pattern of the pyloric region was similar to that of the left leg (Fig. 2, *F*). In three other cases the patterns were qualitatively similar, but the deflections were larger in two (Fig. 2, *G*) and smaller in one. In the other three cases there were minor changes of the QRS pattern in two and slight distortion of the T wave in one (Fig. 2, *D*).

When the exploring electrode was moved to the left side under fluoroscopic guidance, in 10 of these 12 cases the pattern of the QRS complex remained qualitatively the same as in the pyloric region. In nine the deflections were definitely larger (Fig. 2, *F* and *G*), but in one case they were of the same size. In the other two cases the S deflection extended slightly lower, but otherwise the QRS complexes were similar. The T wave was of the same shape in 10 of the 12 cases at the two positions. When the QRS deflections were of greater amplitude, the T wave was also of greater amplitude. In two of the cases in which the QRS complexes were similar, the T wave was somewhat diphasic in tracings made with the electrode situated to the left, whereas it had been a simple upright curve in the lead with the electrode in the pyloric region in one case, and slightly diphasic in the other (Fig. 2, *D*).

In the remaining 24 cases, in which no attempt was made to place the electrode in any particular part of the stomach, but in most of which it lay somewhat to the left, the results were as follows: In three cases the pattern was practically identical with that of the left leg (Fig. 1, *B*). In 12 additional cases the pattern was practically the same qualitatively as that of the left leg, but all the deflections were greater in amplitude (Fig. 1, *A* and *C*). Among the nine cases in which the pattern was classified as different from that of the leg, the QRS complex was similar in five cases, showed minor differences in three (Fig. 1, *D*), and a lack of resemblance in one case only (Fig. 1, *E*). In two of the nine cases, the T wave was similar to that of the leg leads, in five the T wave was diphasic, with the inverted phase first (Fig. 1, *D*), and in two cases there was marked distortion, with RS-T segment deflection (Fig. 1, *E*).

Esophagus.—Studies of esophageal patterns of potential were made in 30 cases. Tracings were made with the exploring electrode at four esophageal positions. The first position was as low as possible. When this could not be ascertained with certainty by fluoroscopic inspection and resistance to pull on the electrode, small amounts of barium sulfate suspension were injected through the tube, so that the tip could be placed in the terminal half-inch of the esophagus. The second position for the exploring electrode was approximately 1 to 1½ inches orad from the first. The third position was at a level about midway between the top and bottom of the heart. The fourth position was level with the top of the auricular shadow. In the first 11 cases the Rehfuss

tip, with its length of 15 mm., was used. In the last 19 cases the tip with the length of 7 mm. was used.

The patterns of ventricular potential variation recorded with the exploring electrode at the third and fourth positions were entirely different from that of the left leg in every case (Fig. 1, *A*, *B*, *C*, *D*, and *E*). The QRS complex was invariably initiated by a large Q wave; in some cases the potential remained negative throughout the entire QRS complex (Fig. 1, *C*), but in others there was a rise above the base line in the latter part (Fig. 1, *A* and *B*). The T wave was either inverted or practically isoelectric in all cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*).

The lower esophageal pattern was practically the same as that of the left leg in two of the cases in which the larger electrode, and six of those in which the smaller electrode, was used, except that the deflections in the esophageal lead were larger (Fig. 1, *A*). In two cases in which the larger electrode, and 10 in which the smaller electrode, was used, there were only minor differences in the QRS or T deflections, or both, from the potential pattern of the left leg (Fig. 1, *D*). In two cases in which the large tip electrode was used, the lower esophageal pattern resembled that obtained at the auricular level (Fig. 1, *C*), and in four the pattern seemed intermediate in type between those recorded with the electrode in the stomach and at the auricular level of the esophagus (Fig. 1, *B*). In these cases the QRS complex was initiated by a Q deflection of considerable amplitude. When the small electrode was placed in the lower part of the esophagus, none of the patterns were the same as those obtained at the auricular level, and, in only two cases, were the tracings intermediate in form between those recorded from the stomach and from the auricular level of the esophagus. In one case in which the larger, and one in which the smaller, electrode was used, the lower esophageal patterns were quite different from those obtained from the left leg, or stomach, and also from those obtained at the auricular level (Fig. 1, *E*). The patterns recorded with the exploring electrode 1 to 1½ inches orad from the lowest part of the esophagus had the following characteristics: When the pattern obtained from the lower esophagus resembled that of the auricular level, the pattern of this position was also similar (Fig. 1, *C*). When the pattern of the lower esophageal level was intermediate in type between the stomach pattern and that of the esophagus at the auricular level, the pattern 1 to 1½ inches orad from the lower portion showed more of the Q deflection. Even when the pattern of the lower esophagus (Fig. 1, *B*) resembled that of the left leg, the pattern 1 to 1½ inches orad showed some of the Q deflection more fully developed at higher levels (Fig. 1, *A*).

DISCUSSION

The data presented above indicate that there is remarkable uniformity in the patterns of potential variation distributed to the left leg, both the anterior and posterior surfaces of the trunk below the level

of the umbilicus,* and the small intestine, including the duodenum. There is no appreciable tendency toward decrement in this pattern of potential variations between a position so near the heart as the descending portion of the duodenum and so far away as the left leg. However, it is of interest that a distinct tendency toward decrement is found on the surface of the back in positions considerably nearer the heart than the left leg.

The correspondence between the patterns obtained with an exploring electrode in the stomach and those recorded with an electrode on the left leg, although remarkably close, particularly in so far as the QRS complex is concerned, is nevertheless not as exact as in the case of the positions discussed above. Wolferth, Livezey, and Wood[2] have pointed out that the preservation of patterns of potential variation throughout extensive regions of the body does not apply to regions very near some part of the external surface of the heart. It had, of course, long been known that tracings made with an exploring electrode on various precordial areas revealed differences in the potential patterns of areas near each other. However, it was also shown that the patterns obtained in experimental animals from positions within the lungs near the heart and near each other differed, and those obtained from positions on the diaphragm near the heart and near each other also differed. Moreover, these patterns obtained from the lower surface of the diaphragm near the heart varied somewhat from the pattern recorded from all other parts of the undersurface of the diaphragm.

In some of the cases studied in this series it was noted fluoroscopically that the exploring electrode was near that part of the diaphragm directly underlying the heart. It was in such cases that the correspondence of the stomach and leg patterns of potential variation was less exact, although even under these circumstances there was usually a fairly close resemblance. In the series of cases in which tracings were made from two stomach positions, the effect of decrement in potential variations as distance from the heart increased was clearly demonstrated. However, in some cases there seemed to be no further decrement between the pyloric region and the left leg.

The distortion of the T wave and the RS-T segment in a few of the electrocardiograms made with an exploring electrode in the stomach and the lower end of the esophagus perplexed us somewhat. It seemed most likely that these changes resulted from adventitious causes. There was no correlation with the level of gastric acidity, and no other reason to believe that there were polarization effects. Because these changes were more likely to be found when the electrode was known to be near the heart, we attributed them to movement of the electrode

*Unpublished studies (Wolferth, C. C., and Livezey, M. M.) made in cases of intraventricular conduction defect and bundle branch block, with their more intricate patterns, confirm the general conclusions derived from this study regarding the distribution of potential on the trunk below the level of the umbilicus, but show that the correlation between patterns on these areas and the left leg is not quite as close as is suggested by studies on normals. In general, the potential variations on the left flank tend to be slightly greater in amplitude than those of the anterior or posterior surfaces of the trunk or the left leg, and those of the right flank are less than those of the other positions.

caused by the heartbeat. This view receives some support from the fact that at, and slightly below, the auricular level in the esophagus, marked deviation from the isoelectric line is sometimes observed just after the "QRS group" of auricular deflections recorded at that level. The fact that such artifacts may occur obviously impairs the value of stomach and esophageal electrocardiograms.

The esophageal electrocardiograms made with an exploring electrode at or slightly below the auricular level bear a resemblance in their general characteristics to those obtained in experimental animals, with an exploring electrode within one or the other ventricular cavity. We are in agreement with the suggestion of Brown,[4] to the effect that, at the auricular level, endocardial potential is tapped by the exploring electrode. At positions between this level and the lower end of the esophagus the effect of this pattern was clearly discernible, in that a Q deflection of considerable magnitude was usually present. At the lower end of the esophagus the pattern found in nearly all cases was one of three types, namely, (1) the diaphragmatic pattern, (2) the "endocardial" pattern similar to that recorded at the auricular level, or (3) a composite pattern intermediate in type between the diaphragmatic and endocardial patterns. Our limited studies suggest that the chance of recording the diaphragmatic pattern of potential in the lower portion of the esophagus is greater when a short electrode is used, but, even with a very small electrode, the endocardial pattern may be recorded from that region.

Consequently, entirely aside from the possibility of artifact in esophageal electrocardiograms, the variability in the types of curves obtained in normals from the lowest part of the esophagus has made us feel that standardization of leads in this area, to the extent that reliable opinions can be formed regarding interpretation, will prove to be extremely difficult, if it can be accomplished at all. Moreover, at present there is very little reason to think that any great advantage is obtained by recording the diaphragmatic pattern in the esophagus in addition to that of the surface of the leg. However, the endocardial pattern recorded at the auricular level cannot be obtained with an exploring electrode on the body surface. Further investigation will be required, particularly in patients with various types of cardiac damage, before a decision can be reached as to whether study of the esophageal pattern at the auricular level has any clinical value aside from study of auricular activity. If not, there will be little reason to think that electrical exploration of the digestive tube adds anything of value to study of the ventricles, over and above what can be learned by placing electrodes on more readily accessible parts of the body.

SUMMARY

1. The pattern of ventricular potential variation distributed to the left leg, which Wolferth, Livezey, and Wood called the diaphragmatic

pattern, is likewise distributed to the anterior and posterior surfaces of the abdomen below the umbilicus, and to the jejunum and the duodenum. It is distributed to the stomach, although, in certain cases, particularly when the exploring electrode is moved to a position directly under and near the heart, the pattern is not faithfully maintained.

2. The amplitude of potential variations does not tend to change materially between a position as near the heart as the pyloric region of the stomach and as far away as the left leg. Decrement between the heart and the posterior surface of the back, however, tends to be greater than that between the heart and the left leg. There is appreciable decrement between the fundus and the pyloric end of the stomach.

3. The pattern of ventricular potential variations recorded with the exploring electrode in the esophagus at the auricular level is similar in its general characteristics to the pattern obtained when an exploring electrode is placed within a ventricular cavity. When an exploring electrode is placed at the lower end of the esophagus, the pattern recorded may resemble either the pattern with widespread distribution below the diaphragm or the "endocardial pattern" recorded at the auricular level, or it may be intermediate in form between these two.

4. When an electrode is placed either in the stomach or esophagus in positions close to the heart, bizarre electrocardiograms are occasionally obtained. These bizarre effects are attributed to movement of the electrode by the heart.

5. The lower end of the esophagus, as judged from a series of controls, is an unfavorable position for the application of the exploring electrode in clinical electrocardiography because of the diversity of patterns found in normals and the apparently hopeless task of standardization of curves for that area. The "endocardial pattern" of potential variation recorded at the auricular level of the esophagus deserves further investigation.

6. We have found no position, or combination of positions, for the application of an exploring electrode below the diaphragm, either on the body surface or within the lumen of the digestive tract, which is superior to the left leg for the study of ventricular electrical activity, although any position below the level of the umbilicus can be used to demonstrate the same pattern.

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A STUDY OF METHODS OF MAKING SO-CALLED UNIPOLAR ELECTROCARDIOGRAMS

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THE almost simultaneous demonstration that chest leads are capable of reflecting the presence of injury in certain parts of the heart when limb leads fail to do so,[1] and that the order of excitation of the human ventricles in bundle branch block can be ascertained by chest leads far better than by limb leads[2] raised new problems in electrocardiography which have not as yet been completely solved. The obvious deficiencies of limb leads and the equally obvious necessity for the use of chest leads, at least as a supplement to limb leads, made it seem desirable to try to learn more about the distribution of potential of cardiac origin on the body surface. Such information is essential if electrocardiographic procedures are to rest upon a scientific basis instead of continuing to rest upon empiricism or unverified assumptions.

In order to study such problems it is first of all necessary to have a method, or methods, by which the potential transmitted to an exploring electrode as a result of cardiac action currents is not materially distorted in electrocardiograms by the potential transmitted to the electrode or system of electrodes with which the exploring electrode is paired. At least three attempts have been made to develop "unipolar" leads in man. The methods used have had to rest upon assumptions, the validity of which remains open to question.

Wilson,[3] in his central terminal method (which, for brevity, we shall refer to as the CT method), subtracts in effect the mean potential of the right arm, left arm, and left leg from that of the exploring electrode. In order to conclude that by such a procedure he records the potential of the exploring electrode, he must assume, as he has pointed out, the validity of the Einthoven equilateral triangle hypothesis.

Molz[4] immersed all of the body except the head in a conducting fluid bath (Leitungswasser) lined by a copper network, and assumed, as the result of experiments with a model, which are not pertinent to the problem, that the potential of the network remained constant.

Eckey and Fröhlich[5] modified Molz' procedure in a variety of ways. The body was completely immersed in distilled water (so that presumably all of the electrolyte in the water was that derived from the body surface) and completely surrounded by a copper network within

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.
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the fluid bath. The proof offered by these workers that the potential of their network remained constant (so that a unipolar lead could be obtained by pairing the network and some body area) was that a difference in potential of cardiac origin could be demonstrated between the copper network and the water inside (which surrounded the body), whereas no difference in potential could be demonstrated between the copper network and the water outside the network. They state that the results obtained by their procedure differed materially from those of Molz, but were in good agreement with those of Wilson's CT method. This latter observation was confirmed by Burger.[6] In a recent paper, Wilson[7] has stated in effect that such studies "demonstrated" that the largest potential variation of the central terminal does not ordinarily exceed 0.3 millivolt. It therefore becomes a matter of some importance to inquire into the validity of Eckey and Fröhlich's procedure in an effort to ascertain whether Wilson's method, which at least has the advantage of being practical for clinical electrocardiography, may be accepted as valid, or whether both procedures are still to be regarded as open to question.

EXPERIMENTS ON ECKEY AND FRÖHLICH'S IMMERSION PROCEDURE FOR OBTAINING "UNIPOLAR" LEADS

An enameled pan approximately 20 inches long, 8 inches wide, and 6 inches deep was filled nearly to the top with distilled water. A sheet of bronze fly-screening was molded into the form of a bowl with a diameter at the top of approximately 6 inches. It was placed in the distilled water bath, the sides of the screen being high enough so that the water inside was completely screened from the water outside. The screen was insulated from the pan by rubber sheeting. The right arm lead wire of the electrocardiograph was attached to the screen. The forefingers of both the right and left hands were placed in the bath inside the screen about 5 inches apart, near opposite sides of the screen, and an electrode attached to the left arm lead wire was placed in the bath inside the screen about ¼ inch from the forefinger of the right hand. The sensitivity of the apparatus was adjusted so that 1 mv. = 3 cm. The tracing obtained is shown in Fig. 1, *A-1*. The left arm electrode was then removed to the bath outside the screen, under which circumstances no difference of potential developed (Fig. 1, *A-2*).

The above results are identical in principle with those obtained by Eckey and Fröhlich[5] with respect to the potential of the network and the water inside and outside the network, and constitute all of the evidence adduced by these authors to demonstrate that the potential of the network remains constant. If such evidence proves that the potential of the network in Eckey and Fröhlich's procedure remains constant despite the fact that a human body was inside their network, it would also prove that the potential of our screen remains constant when

a part or parts of the body are in contact with the water inside the screen. As a matter of fact, the evidence cited above does not prove that the potential of Eckey and Fröhlich's network or of our screen remains constant, but is irrelevant to that problem. There is reason to predict that, in the Eckey and Fröhlich procedure, the relative nearness of a part of the body to the screen will influence the differences of potential of cardiac origin which develop between the surface of such a part and the screen. If this is the case, the procedure is obviously useless as a method for making unipolar electrocardiograms. The probability of occurrence of this phenomenon can be tested by a simple experiment, using the model we have described above.

A long needle electrode, insulated except at the tip and connected with the right arm lead wire, was strapped to the right forefinger in such a way that, when the finger was placed in the water bath, the electrode was completely insulated from the bath. Thus, the finger constituted the sole source of potential variation of cardiac origin transmitted to this electrode. An electrode attached to the screen was connected with the left arm lead wire. Both the right and left forefingers were placed near the middle of the water bath inside the screen, each to a depth of approximately 1 cm., and approximately 1 cm. from each other, and an electrocardiogram was made (Fig. 1, *B-1*). The right forefinger, inserted to approximately the same depth as before, was then moved to within 1 cm. of the edge of the screen, and the electrocardiogram was repeated (Fig. 1, *B-2*).

The above experiment demonstrates that, despite the fact that no differences of potential developed between the screen and the part of the water bath outside the screen (tested in each instance as in Fig. 1, *B-3*), moving the right forefinger from a position near the middle of the part of the bath inside the screen to a position much nearer a part of the screen, while the left forefinger remained in a relatively constant position, caused definite changes in the differences of potential between the right forefinger and the screen. Whether these changes are due to changes in the potential variations of the electrode attached to the screen, or the electrode attached to the finger, or both, is of no great importance in so far as the validity of the method is concerned. The fact that the electrode on the finger was insulated from the water suggested that the change in potential variations was in the electrode attached to the screen. This view is supported by various other experiments, of which one is described herewith.

If an electrode attached to the left leg is connected with the left leg lead wire, and an electrode attached to the screen is connected with the right arm lead wire, and the right forefinger is placed in the part of the water bath inside the screen, an electrocardiogram made under such conditions resembles Lead II (Fig. 1, *A-3* and *A-4*). If, however, the

right forefinger is replaced by the left forefinger, the electrocardiogram resembles Lead III (Fig. 1, *A*-5 and *A*-6). These results are what one would expect if the potential variations of the finger in the bath were transmitted to the screen. They would be difficult to explain in any other way.

From the observations in the various experiments described above, it seems to us proper to conclude that the reason advanced by Eckey and Fröhlich to support the claim that their immersion procedure can be used to obtain unipolar leads has no merit. We are therefore not greatly moved in favor of the CT procedure by Wilson's assertion that studies made by Eckey and Fröhlich's procedure "demonstrated" that the potential variations of the central terminal do not usually exceed 0.3 millivolt. The current flow in water with a low electrolyte content and in a network seems to be about what would have been anticipated from established laws of physics.

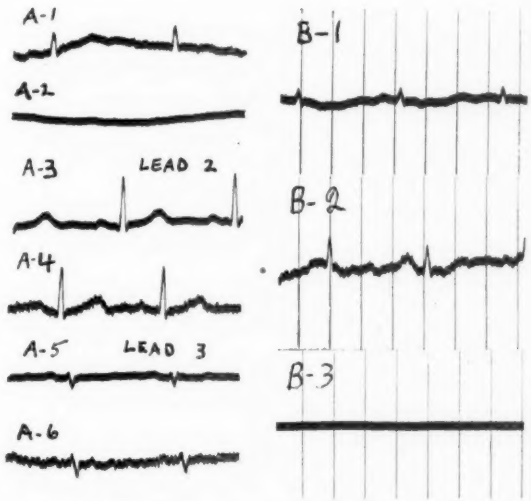

Fig. 1.—See text for explanation of illustrations.

The dubious status of Eckey and Fröhlich's procedure emphasizes the importance of attempting to obtain at least some evidence bearing on the accuracy of Wilson's CT method before accepting it. It occurred to us that there might be some value in comparing certain results obtained by CT "unipolar" leads with those obtained by pairing the exploring electrode with one placed over the spine of the right scapula (which, for brevity, we shall call the RS method). This latter procedure, as we have demonstrated by comparison with the method of balanced potentials,[8, 9] produces less subtraction or interference effects on the potential variations of the exploring electrode than is produced by pairing it with either the right or left arm.

COMPARISON OF THE CENTRAL TERMINAL METHOD FOR RECORDING THE POTENTIAL VARIATIONS OF AN EXPLORING ELECTRODE WITH THE METHOD OF PAIRING THE EXPLORING ELECTRODE WITH ONE PLACED OVER THE SPINE OF THE RIGHT SCAPULA

In 1934, when Wilson and his associates[10] reported studies of bundle branch block in which the CT method was used, the following statements appeared: "A second peculiarity of the precordial curves in right branch block is the prominent upstroke at the beginning of QRS in the leads taken furthest to the right. This deflection occurs in canine as well as in human curves. No similar deflection is present in direct curves from the right ventricle of dogs with right branch block. For the time being the origin of this summit remains obscure." The upstroke referred to in the above quotation, because of the polarity used at that time, represents relative negativity of the exploring electrode, and would be a downstroke with the polarity used at present. In a recent paper by Wilson and his associates,[7] in which the electrocardiographic abnormalities in right bundle branch block are described, we were unable to discover any reference to the unexplained deflection in leads made over the right side of the precordium by the CT method. It is nevertheless well illustrated in Figs. 11, 12, 14, and 15 of that paper. We shall attempt to show in a part of the evidence to be presented that this deflection has a significant bearing on the validity of Wilson's "unipolar" leads.

It is generally assumed that the potential variations of an epicardial area are so much greater than those of other parts of the body away from the heart that leads made with one electrode on the epicardium and the other on some area away from the heart are in effect unipolar leads.[7] This view is supported by the fact that the position of the distal electrode has little influence on the form of such an electrocardiogram. On the other hand, a change in the position of the distal electrode is capable of modifying the form of the *precordial* electrocardiogram, although in general these curves are determined mainly by the position of the exploring electrode. It is also assumed by many workers, both from theoretical considerations and from the results of experimental observations, which need not be reviewed here, that the potential of a precordial area is dominated by the action currents flowing in the part of external cardiac surface nearest to it. We know of no evidence not in accord with this assumption. Obviously, however, one would expect decrement in the magnitude of potential variations as the distance from the heart increases (which seems to have been clearly confirmed by experiment), and, equally obviously, the ratios of distance between the electrode and various parts of the heart are altered as the electrode is moved from contact with the heart to some point farther away. Thus, while there may be a resemblance between an epicardial lead and one

from the overlying precordium, they may have important differences qualitatively as well as quantitatively. It follows, therefore, that a material difference in form between an epicardial and overlying precordial lead may result from (1) a difference in the potential variations transmitted to the exploring electrode because of the fact that, when electrodes of the same size are used, the precordial electrode is materially influenced by a relatively larger area of the epicardial surface, or (2) in precordial leads, the distal electrode or set of electrodes may no longer be relatively indifferent, so that the precordial lead is, to a certain extent, a subtraction or interference curve.

The second of the above-mentioned possibilities, namely, that Wilson's "unexplained deflection"[10] is derived from the central terminal, does not seem to have been tested. If evidence could be obtained that the potential of the central terminal does not remain constant during the heartbeat, it would open to question the value of Wilson's method for recording the potential variations of single areas, and particularly of positions so far from the heart as the extremities. Thus, Wilson's conclusion that the potential of the right arm is conspicuously negative throughout the greater part of the QRS interval might be one of a series of incorrect statements. This is due to the fact that, when the exploring electrode is placed at a distance from the heart, the form of the electrocardiogram might not only be influenced by the potential variation of the central terminal, but might actually be dominated by it, if the potential variation transmitted to the exploring electrode happened to be of relatively small magnitude. It is of vital importance to electrocardiography that, if error in matters of this nature exists, such error be recognized. If, on the other hand, there is no important source of error in Wilson's "unipolar" leads, they should be used for practically all electrocardiographic work. We shall therefore inquire into the credibility of assumptions which must underlie "unipolar" leads and also those which must underlie our RS method. We shall then present the results of certain tests of the ability of these methods to demonstrate distribution of potential variation in accord with the underlying assumptions.

The Assumptions Underlying the RS and CT Methods.—We have emphasized in previous publications[8, 9] that two assumptions have to be made to establish our balanced potentials procedure and its simpler substitute of pairing the exploring electrode with one placed over the spine of the right scapula (RS method) as methods of recording the potential variations of an exploring electrode. The first is that an approximate balance of potentials among the positions on which electrodes are placed, with their varying patterns of potential variation, cannot occur consistently by chance throughout the entire ventricular complex, although it might readily occur by chance at a single instant. It has seemed to us to be safe to make this assumption. The second assumption is that, along surface lines extending from the right and left

borders of the heart to the corresponding shoulder, there is no part of the potential variation that is not subject to decrement as distance from the heart increases. It is recognized that the validity of this second assumption does not have to be conceded. The magnitude of the error involved in this assumption measures the error of the method of balanced potentials as a unipolar procedure (plus a slight additional error, usually not exceeding 1 mm. for any part of the ventricular complex, because of the combination of technical fault and discrepancy between the prediction of accurate preservation of pattern and experimental observations).

It is essential to the Einthoven equilateral triangle hypothesis that the trunk function as a homogeneous fluid volume conductor, and it is therefore inevitable, if that hypothesis be valid, that all potential variations be subject to decrement as distance from the heart increases.[11] Consequently, our second assumption is a necessary part, but by no means the whole, of only one of the assumptions which underlie the CT method. If our assumption, which, however, does not require that the body function as a homogeneous fluid volume conductor, is not valid, neither procedure requires further consideration. If, on the other hand, the second assumption we have made is valid and the results obtained by this method and Wilson's CT method differ materially—which they do in most cases*—there seems to be no possibility that the assumptions which underlie the Einthoven hypothesis are all valid, or that the CT method is justified.

Among the various reasons for suspecting that the Einthoven hypothesis is subject to enormous error are the easily demonstrable differences in decrement of potential variation above and below the diaphragm as distance from the heart increases. We have already published studies which illustrate this fact in man, and have shown in experimental animals that there is comparatively little decrement between positions so near the heart as just below the diaphragm, and the left leg,[9] although, in man, there may be appreciable decrement on the surface of the back.[12] Against this may be contrasted the very rapid decrement found on the front of the chest[8, 9] or in the esophagus above the level of the heart. The distribution of potential on the upper part of the human abdomen seems to be complex, but there is definite evidence to indicate that in this area there is rapid decrement of the precordial patterns as distance from the heart increases. In the same area there is probably fairly uniform distribution of the diaphragmatic pattern, similar to the distribution of this pattern to other positions below the diaphragm in man and to the entire body surface below the diaphragm in dogs.[9] If this be the case, we have one pattern of potential fairly uniformly distributed on the upper part of the abdomen, and another subject to rapid decrement. This behavior raises a question as to the

*The potential of Wilson's central terminal and that of an electrode over the spine of the right scapula are occasionally nearly the same throughout either the QRS complex or the T wave, but rarely throughout both.

justification of an assumption that there is no uniform distribution of a potential pattern to all regions above the diaphragm. Such an assumption, if valid, would mean, as stated above, that approximately unipolar leads could be recorded by the method of balanced potentials. If it is not valid, the method of balanced potentials merely reduces interference with the potential variations of the exploring electrode by eliminating the potential variations concerned in the formation of Lead I, irrespective of whether the electrodes by which the balance is achieved are on the right or the left side.

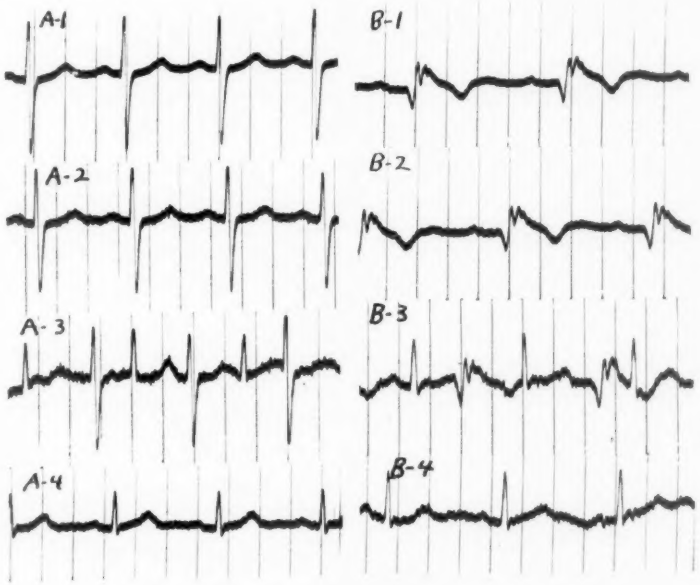

Fig. 2.—*A-1* is the CR_4 lead of Subject 1. In *A-2*, the electrode was removed from the precordium of Subject 1 and was placed on the right arm of Subject 2; contact between the two subjects was maintained by placing the right forefinger of Subject 2 on the C_4 chest position of Subject 1. In *A-3*, the contact between the two subjects was maintained, but the electrode was moved from the right arm to the left leg of Subject 2. In *A-4*, the electrode which, in the preceding experiments had been on the right arm of Subject 1, was removed to the right arm of Subject 2, thus recording Lead II of that subject.

In the *B* series the same set of experiments was performed except that the C_2 chest position was used for the point of contact between the two subjects. Subject 1 of these experiments had a typical right bundle branch block. These observations show that the potential variations of the point of contact of each subject with the other are uniformly distributed throughout the body surface of the other subject. Apparently each body functions as a nonpolarizable electrode for its area of contact with the other subjects.

If it be assumed that there is uniform distribution of a potential pattern to all positions above the diaphragm, this pattern is not eliminated by the method of balanced potentials, and is therefore also present but not recognized over the spine of the right scapula. Such a pattern will be subtracted quantitatively from the potential variations of an exploring electrode in electrocardiograms made when the latter is placed below the diaphragm. Unless the pattern uniformly distributed above the diaphragm is qualitatively the same as that below the diaphragm, however, the configuration of the electrocardiogram must necessarily

change as the amplitude of recorded deflections increases or decreases. Studies of the intricate patterns of bundle branch block made in our laboratory by the RS method, which tend to exhibit relatively smaller deflections in the right flank and back and slightly larger deflections in the left flank than in the left leg, show excellent preservation of pattern in all these positions. In the recent study referred to above,[12] it has been demonstrated by the RS method that the pattern recorded from the left leg and from positions so near the heart as the fundus of the stomach or the lower end of the esophagus may be practically identical, except for a marked increase in the size of deflections at positions near the heart. These observations would seem to rule out the likelihood, although not the possibility, that any pattern other than the one recorded is concerned.*

One of the assumptions required by the Einthoven hypothesis is that the attachments of the extremities are far enough away from the heart that electrical activity in one part of that organ possesses no advantage, by virtue of its relative distance, over electrical activity of any other part in exerting an influence on the potential variations of an extremity. We have shown by the method of balanced potentials, by the RS method, and by pairing the electrodes about the attachments of the arms† that the pattern of potential variations of the right arm is usually similar to that of the right side of the precordium, except that the deflections are very small.[8, 9] It was shown by the same methods that the pattern of potential variation of the left arm is similar to that obtained from a position just outside the left border of the heart. Moreover, as was stated above, it has been shown by the RS method that the pattern of potential variations of the left leg is similar in the great majority of cases to the pattern recorded from the duodenum or from parts of the stomach, and not infrequently to patterns recorded from the lower end of the esophagus.[12] Furthermore, cardiac injury leading to the development of abnormality in one of these patterns does not necessarily cause abnormality in the other patterns (unpublished observations). Such relations we regard as one of the many observations which are incompatible with the Einthoven hypothesis.

*Potential variations uniformly distributed throughout areas to which electrodes are applied obviously cannot be detected, for we measure only difference of potential. This fact exposes to error any so-called unipolar lead made under conditions where such a possibility exists. This can be demonstrated by the following simple observation. If contact is made between two subjects with skin resistance low enough for currents to flow freely, the mean potential of that part of one subject in contact is uniformly distributed throughout the other subject. This phenomenon is not detected by any method of pairing electrodes on one subject alone. It is necessary to place the exploring electrode at the point of contact, and after contact has been made, at various positions on the body of the second subject, observing the similarity of patterns recorded (with such connections on the two bodies, an electrocardiogram of the second subject will also be recorded). These phenomena are illustrated in Fig. 2.

†This procedure corresponds in principle to Groedel's partial electrocardiograms,[10] which led him to conclude that the potential of the right arm is derived from the right ventricle, and that of the left arm from the left ventricle. In reality, the potential variations of the right arm are dominated by the action currents occurring at the anterior surface of the right ventricle (which in turn are derived in part, at least, from electrical activity in the left ventricle), and the potential variations of the left arm are dominated by the action currents at the anterolateral wall of the left ventricle (which likewise are derived in part from activity in the right ventricle).

Studies on the electrical characteristics of tissues[13-15] in attempts to obtain evidence whether they behave in a manner consistent with the assumption that the body functions as a homogeneous fluid volume conductor have led to conclusions which are not in full agreement. In fact, only one of these studies[15] seems to offer any support to the assumption, but since no attention is paid to the relationships of tissues to each other as they occur in the human body, the possible significance of that study from our present viewpoint remains to be decided.

From the foregoing discussion, we conclude that such tests as have been made of the assumptions required to support the prediction that the mean potential of the right arm, left arm, and left leg will remain approximately equal to zero throughout the cardiac cycle,* instead of confirming the validity of that prediction, tend to increase the doubt concerning it. It is therefore necessary to obtain further evidence, which can be done by direct comparison of some of the data obtained by the CT and RS methods in a study of the distribution of potential of cardiac origin.

Comparison of Results Obtained by RS and CT Methods.—In the observations to be reported below, in which certain results of the two methods are to be compared, both the central terminal and an electrode on the spine of the right scapula were paired with the same exploring electrode so that there could be no question as to the sources of differences in the tracings or the time incidence of deflections. A resistance of 50,000 ohms was interposed between each of the electrodes connected with the central terminal and the terminal itself. Three types of observations were made in this study.

Observation 1.—If the unexplained upward (downward, according to the polarity used at present) deflection recorded from the right side of the precordium in right bundle branch block results from potential variations of the central terminal, the following may be expected to be true:

a. The unexplained deflection will not be subject to decrement as the exploring electrode is moved toward the right shoulder, although the potential transmitted to the exploring electrode may be subject to decrement.

b. The differences in potential between the central terminal and a relatively more constant potential will include part or all of the unexplained deflection.

c. The potential variations of the right side of the precordium recorded by a more accurate method should resemble those found over the epicardium of the right ventricle of the dog more closely than those of the CT method, in that the unexplained deflection will be either absent or smaller.

*The sum of the differences of potential between the central terminal and electrodes on each of the three extremities obviously must equal zero. Failure to take into account this simple mathematical relationship might lead one to think that he had experimental confirmation of the validity of the CT method.

In Fig. 3 the following points, representative of results in six cases, are illustrated:

1. The "unexplained deflection" is present in a case of right bundle branch block, just as Wilson[10] found it when the right side of the precordium is paired with the central terminal (*A-1*). It does not decrease in size as the exploring electrode is moved to successive positions farther from the heart in the direction of the right shoulder,* although the other parts of the QRS complex are subject to decrement (*A-2* and *A-3*). On the right arm this unexplained deflection is greater in amplitude than any other deflection of the QRS complex, and actually dominates the pattern (*A-4*).

2. The unexplained deflection is present in a lead made by the CT method with the exploring electrode placed over the spine of the right scapula (*B* series).

3. Leads made by the RS method with the exploring electrode on the C_1 position, the right arm, and intermediate positions fail to show the unexplained deflection, and, to this extent, resemble the tracings which Wilson obtained from the right side of the heart in canine bundle branch block (*A* series).

Observation 2.—Decrement as an exploring electrode is moved from the right side of the precordium in the direction of the right shoulder can be demonstrated by any method of pairing electrodes, provided the distal electrode or set of electrodes is placed at a distance from the heart. If the distal electrode makes a contribution to the electrocardiogram, this contribution will be relatively greater as distance of the exploring electrode from the precordium increases and interference with the pattern of the exploring electrode correspondingly increases. Consequently, the method by which integrity of patterns is best maintained probably records tracings with the least interference from the distal electrode or central terminal. Figs. 3 and 4 illustrate the superiority of the RS method over the CT method in reflecting the integrity of pattern as the distance of the exploring electrode from the heart increases (Figs. 3, *A*, *C*, and *D* series. Fig. 4, *A*, *C*, and *D* series).

Observation 3.—If electrodes are paired by placing the distal electrode on the tip of the right acromial process and the exploring electrode on the right anterior axillary fold, the resulting electrocardiogram resembles the pattern of potential variations of the right arm as obtained by the RS method, and usually does not resemble the pattern obtained by the CT method (Figs. 3, *A-4* and *A-5*, *D-4* and *D-5;* Fig. 4, *A-3* and *A-4*, *C-4* and *C-5*). Similar relationships are found when electrodes are paired in the same way about the attachments of the left arm. The agreement between RS and CT methods is better for the left arm than the right because the potential variations of the left arm are usually greater, and the potential variations of the "indifferent electrode" are

*It actually seems to increase in size because of lessening of the neutralizing effect of positive potential variation derived from the exploring electrode.

relatively less able to distort the pattern of the exploring electrode (Fig. 3, *C* series).

DISCUSSION

In the past there has been no means by which the probable validity of the CT method of making unipolar leads could be tested, although attempts have been made to use the immersion procedures for that purpose. There is no completely satisfactory method now, and perhaps because of the impossibility of being certain that one is recording the potential variations of a single electrode, none can be devised with apparatus now available. Nevertheless, as we have tried to show, it is possible, by comparing certain differences in results obtained by the CT and RS methods, to secure data which have a definite bearing on the validity of the two procedures. In this study we have concentrated our attention, as discussed in detail below, on (1) the comparative ability of the two methods to demonstrate preservation of certain patterns of potential variation as recorded from positions near the heart and from other positions much farther from the heart, (2) a comparison of the results obtained in recording the potential variations of the upper extremities by these methods and by pairing electrodes across the attachments of the arms, and (3) the behavior of Wilson's "unexplained deflection" in right bundle branch block,[10] as illustrated by the CT and RS methods.

1. Both methods can be used to demonstrate that, along a line from the right side of the precordium to the right shoulder and a similar line from just outside the left border of the heart to the left shoulder, decrement in potential variations occurs as distance from the heart increases, and that there is a tendency toward preservation of a pattern recorded near the heart. The superiority of the RS method over the CT method in preserving the pattern at positions along both lines is illustrated in Figs. 3 and 4. If one is to assume that the CT method is the more accurate of the two, one must also assume that the better preservation of the pattern by the RS method is a remarkable coincidence resulting from the interference of potential variations derived from the electrode placed over the spine of the right scapula. It would probably be conceded that no great error is involved in regarding the pattern of potential variations transmitted to the latter electrode as similar for each heart beat. If so, we believe there would be considerable difficulty from the mathematical viewpoint in defending the assumption that the preservation of the pattern with decrement results from interference arising from the electrode placed over the spine of the right scapula. Thus, it seems safe to conclude that decrement with preservation of pattern must reflect potential variation of the exploring electrode. On the other hand, there are no difficulties encountered in the assumption that the inferiority of the CT method for the demonstration of preservation of patterns with decrement results from a

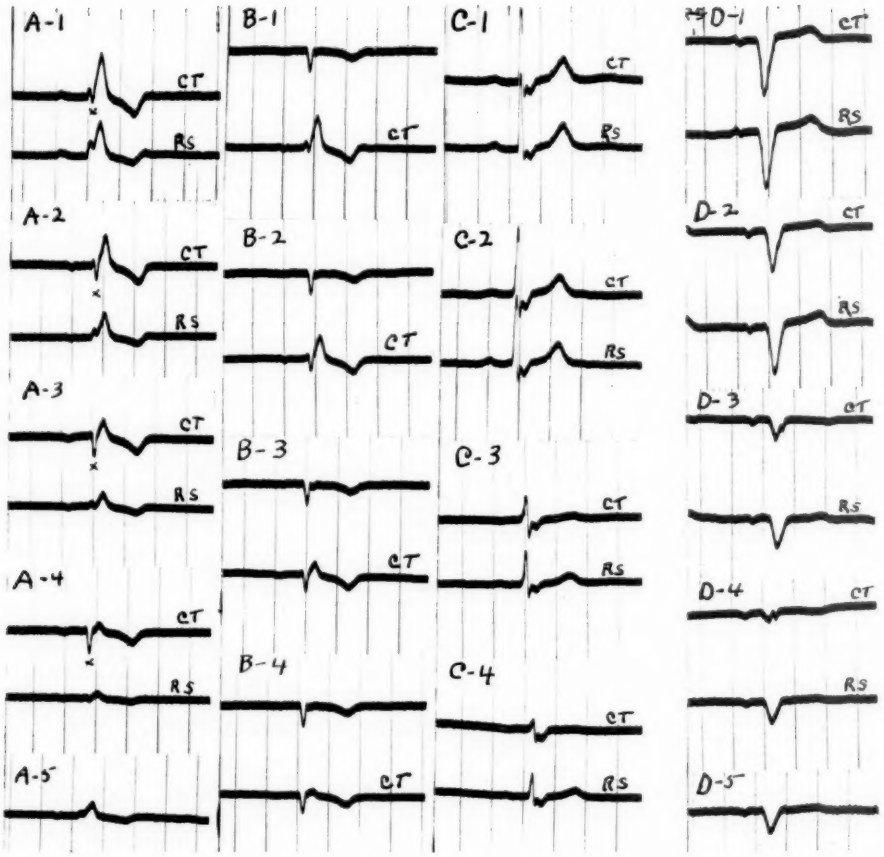

Fig. 3.—All of the tracings in series *A*, *B*, and *C*, were made from a patient with right bundle branch block. In *A-1*, the exploring electrode was placed on the C_1 chest position and paired both with the central terminal CT (50,000 ohms resistance being interposed between each electrode on a limb and the central terminal in all experiments) and with an electrode on the spine of the right scapula, RS. Note the "unexplained" early deflection, marked "*x*" in the CT lead. In *A-2*, the exploring electrode was moved 1½ inches in the direction of the right shoulder, in *A-3* an additional 1½ inches, and, in *A-4*, it was placed on the right arm. In *A-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode over the tip of the right acromial process.

In the *B* series, the central terminal leads, CT, were made like those of the *A* series, and each was recorded simultaneously with a CT lead made with an exploring electrode on the spine of the right scapula. The "unexplained" deflection constitutes the only major difference of potential, during the QRS complex, between the central terminal and the spine of the right scapula.

In *C-1*, the exploring electrode was placed slightly above and to the left of the C_5 chest position, and paired with the central terminal, CT, and the spine of the right scapula, RS. In *C-2*, the exploring electrode was moved 1½ inches in the direction of the attachment of the left arm, in *C-3*, 1½ inches further in the same direction, and, in *C-4*, on the left arm.

The tracings in the *D* series were obtained from a patient with left bundle branch block. In *D-1*, the exploring electrode was placed on the C_1 chest position, and paired with the central terminal, CT, and the spine of the right scapula, RS. In *D-2* and *D-3*, the exploring electrode was moved to successive positions 1½ inches nearer the attachment of the right arm, and, in *D-4*, it was placed on the right arm. In *D-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode over the tip of the right acromial process.

constant error caused by the recurrence of potential variations in the central terminal. On the basis of this assumption, the smaller the potential variations of the exploring electrode become, the greater the distortion of the pattern, which is in agreement with the experimental data.

2. In Figs. 3 and 4 the comparison between the patterns of differences of potential recorded by pairing electrodes across the attachments of

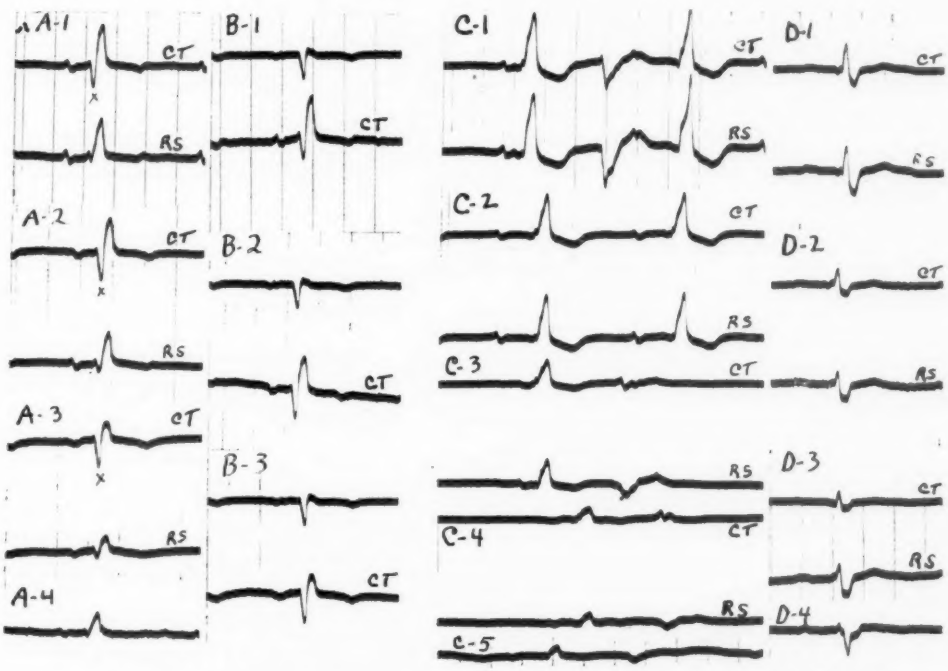

Fig. 4.—The tracings in the *A* and *B* series were obtained from a patient with right bundle branch block. In *A-1*, the exploring electrode was placed on the C_1 chest position and paired with the central terminal, CT, and with an electrode on the spine of the right scapule, RS. In *A-2*, the exploring electrode was moved to a position approximately midway between the C_1 chest position and the attachment of the right arm, and, in *A-3*, it was placed on the right arm. In *A-4*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode on the tip of the right acromial process. Note that there is a large "unexplained" deflection "*x*" early in the QRS complex of the CT leads and a small "unexplained" deflection in RS leads, neither of which is subject to decrement as the exploring electrode is moved farther from the heart, and that this deflection is insignificant in the lead made by pairing electrodes across the attachments of the right arm.

In the *B* series, the CT leads were made as in the *A* series. The upper lead of each group was obtained by pairing an exploring electrode on the spine of the right scapula with the central terminal. The "unexplained" deflection represents the chief difference of potential between the central terminal and the spine of the right scapula, although the T-wave potential of the latter position is relatively slightly negative to that of the central terminal. The tracings in the *C* and *D* series were obtained from a patient with right bundle branch block and ventricular extrasystoles. In *C-1*, the exploring electrode was placed on the C_1 chest position, and paired with the central terminal, CT, and with an electrode over the spine of the right scapula, RS. In *C-2*, the exploring electrode was moved 1½ inches in the direction of the attachment of the right arm, in *C-3*, 1½ inches further in the same direction, and, in *C-4*, to the right arm. In *C-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode placed over the tip of the right acromial process.

In *D-1*, the exploring electrode was placed on the C_5 chest position, and paired with the central terminal, CT, and with an electrode over the spine of the right scapula, RS. In *D-2*, the exploring electrode was placed midway between the C_5 chest position and the attachment of the left arm, and, in *D-3*, on the left arm. In *D-4*, the exploring electrode was placed on the left leg and paired with an electrode placed over the spine of the right scapula. In this case, the potential variations of the right arm, left arm, and left leg, as recorded by the RS method, are such that the mean potential variation of the three would be small. This probably accounts for the relatively good correspondence obtained by the two methods in the case of supraventricular beats.

one of the upper extremities (anterior axillary fold and tip of acromial process) and patterns of potential variations of the corresponding area recorded by the RS and CT methods is illustrated. These are representative of results in a large series of cases (not reported here). Almost invariably there is good correspondence with the RS method for both extremities. In some cases there is fairly good correspondence with the CT method on the left side, but there is little resemblance between the two types of tracing on the right side. If it is assumed that the CT method is truly unipolar, the better correspondence between the "partial electrocardiograms" made with electrodes paired across the attachments of the arms, and the RS method for recording the potential variations of the arms must be assumed to be due to error in the method, resulting from the fact that potential variations transmitted from the spine of the scapula cause this better correspondence. Conceivably, this might apply on the right side because the difference in potential between the surfaces over the tip of the right acromion and the spine of the right scapula is slight. This explanation, however, would not apply to the better correspondence observed on the left side. A more probable explanation for these discrepancies would seem to be that the potential variations of the central terminal are greater than those of an electrode placed over the spine of the right scapula.

3. Analysis of the behavior of the "unexplained" deflection described by Wilson as being recorded over the right side of the precordium in right bundle branch block by his CT method offers, we believe, the most instructive comparison of the CT and RS methods. We have pointed out that this deflection, recorded, according to Wilson, from the right side of the precordium both in dogs and man in right bundle branch block, but not from the surface of the right ventricle in dogs, might therefore be derived from the central terminal. The fact that the unexplained deflection is either not recorded at all or is of relatively small magnitude when the potential variations of the right side of the precordium are recorded by the RS method does not tend to lessen that suspicion. The further facts that all of the deflections recorded by the RS method are subject to decrement as the electrode is moved toward the right shoulder, and that all of those recorded by the CT method except the unexplained deflection are also subject to decrement can be accounted for in only one of two ways. If the unexplained deflection is derived from the central terminal, one would expect no decrement as the electrode is moved farther away from the heart because the potential variations of the central terminal would not vary materially. If, on the other hand, it is transmitted by the exploring electrode and is not subject to decrement as the distance from the heart increases, it does not behave in accordance with the distribution of potential to be expected in a fluid volume conductor. If, therefore, we accept the Einthoven equilateral triangle hypothesis, we are forced to

the contradictory conclusions that the "unexplained" deflection (1) cannot be derived from the central terminal,[3] and, (2) because of its lack of decrement at positions far from the heart, cannot be derived from the exploring electrode.[11] To avoid such an absurdity, we must discard the Einthoven hypothesis, and, with it, the sole reason for believing that the central terminal procedure ever records unipolar leads except by chance. That it actually does occasionally achieve this result with substantial accuracy in certain cases of right bundle branch block, in which the "unexplained" deflection is not recorded, we believe we have shown in Fig. 4, series *C*. Here, decrement with preservation of pattern as the distance of the exploring electrode from the heart increases is shown as well by the CT as by the RS method, in so far as beats of supraventricular origin are concerned. The CT method, however, is far inferior in demonstrating preservation of the pattern of the ventricular extrasystoles which interrupt the normal rhythm. It would appear, therefore, that the above is purely a chance result, and does not even apply to two different pathways of excitation in the same case.

If, as the evidence appears to indicate, the unexplained deflection is derived through the central terminal, the further question arises as to its source. We have made no special effort to solve this problem, but the following facts have emerged as by-products of our studies. This deflection does not appear in CR_1 leads in right bundle branch block. A somewhat similar, but small, deflection may appear in CF_1 leads, but the time relations of this deflection may be slightly different from those of the unexplained deflection. The CL_1 lead usually shows an unexplained deflection with identical time relations and with a magnitude more than twice as large as that of the central terminal lead with the exploring electrode on the same position. When extensive infarction of the left ventricle has occurred, so that the preintrinsic-intrinsic-like pair of deflections disappears from leads made with an exploring electrode placed over the left border of the precordium, the CL_1 lead may fail to show an unexplained deflection. Under these circumstances the central terminal procedure fails to record an unexplained deflection (as in Fig. 4, *C* series) or, at most, records a very tiny one. These data suggest, but do not prove, that the unexplained deflection is a left ventricular phenomenon which exerts an effect on the potential variations of the central terminal, mainly via the left arm electrode.

If we are justified in concluding that the unexplained deflection recorded over the right side of the precordium in right bundle branch block is a left ventricular phenomenon exerting its effect on leads made by the CT method via the central terminal, it would follow, because potential variations derived from the left ventricle are not usually greatly changed in right bundle branch block, that a similar error probably exists in normal cases. In our opinion, therefore, Wilson's[7] statement to the effect that the potential of the right arm is negative

throughout most of the QRS interval may be based in part on failure to take into account the possibility that a potential variation similar in magnitude to that which produces the unexplained deflection is contributed by the central terminal.

Electrocardiography has always suffered from the handicap that its results represent differences between two unknown variables. There is reason to believe that this handicap is not so serious in the case of chest leads as in the case of limb leads because of the relatively greater magnitude of potential variations at chest wall positions. Nevertheless, the possibility of error, even in chest leads, in ascribing the source of potential variation to one electrode, when, in fact, it is attributable to the other, has been demonstrated in this paper. The struggle toward the objective of an approximately accurate unipolar lead is far from over, and perhaps it has just begun. If the method of balanced potentials and its simpler, although slightly less accurate, substitute of pairing the exploring electrode with one over the spine of the right scapula, marks any progress toward that objective, it can only be so because the assumptions which underlie those procedures are valid. It is at this point that the most searching examinations of this procedure, as well as procedures that are called unipolar leads, must be made.

SUMMARY

1. The reason given by Eckey and Fröhlich for stating that unipolar electrocardiograms can be obtained by their procedure of immersing the body in distilled water and surrounding it by a copper network which is also in the water bath, with one electrode on a body area paired with an electrode attached to the network, has been subjected to experimental test. Evidence is furnished that this reason is not valid. There is, consequently, no ground for believing that unipolar electrocardiograms can be obtained by such a method.

2. The central terminal procedure of Wilson for making unipolar leads has been subjected to study.

A. The good agreement which is said to exist between Wilson's central terminal procedure and Eckey and Fröhlich's immersion procedure, a point made by Wilson in support of his method, does not demonstrate the validity of the central terminal procedure because the principle underlying the immersion procedure is unsound.

B. The various assumptions which have to be made if the central terminal procedure is to be regarded as valid as a method for making unipolar leads were compared with the assumptions which have to be made to establish the method of balanced potentials (or its simpler but slightly less accurate substitute of pairing the exploring electrode with one placed over the spine of the right scapula) as a procedure for (1) making unipolar leads, or (2) reducing interference with the potential variations of the exploring

electrode. Certain observations regarding the distribution of potential on the surface of the body cannot be accounted for on the basis of the assumptions which must underlie the central terminal procedure. No such difficulties were encountered regarding the less elaborate assumptions underlying the other procedures.

C. Certain comparisons of results obtained by the central terminal method and by pairing the exploring electrode with one placed over the spine of the right scapula have been made. (1) The latter procedure shows the phenomenon of decrement with preservation of pattern as the exploring electrode is moved away from the heart along certain lines far better than does the central terminal method; (2) the correspondence of patterns of difference of potential recorded by pairing electrodes across the attachments of the right and left arms with the patterns obtained by placing one electrode on the arm of the same side and the other on the spine of the right scapula is far closer than the "unipolar" patterns of arm potential obtained by the central terminal method, and (3) a negatively directed deflection recorded early in the QRS complex by the central terminal procedure at the C_1 position in most cases of right bundle branch block is recorded as a very small deflection, or not at all by the RS procedure. This deflection, unlike other parts of the QRS complex, is not subject to decrement as the exploring electrode is moved away from the heart. All the evidence indicates that it is derived from the central terminal. Moreover, if the assumptions which must underlie the central terminal procedure are valid, it is impossible to account for the derivation of such a deflection from either the central terminal or the exploring electrode.

3. The evidence presented indicates that, by pairing an exploring electrode with one placed over the spine of the right scapula, less interference with the potential variations of the exploring electrode occurs than in the case of methods which have been called unipolar. The bearing of this conclusion, if it be valid, on methods used in clinical electrocardiography is obvious.

We wish to thank Drs. J. H. Austin, Director of the William Pepper Clinical Laboratory, University of Pennsylvania, and L. I. Schiff, Assistant Professor of Physics, University of Pennsylvania, for valuable criticism and advice, and Dr. Franklin D. Murphy, Instructor in Medicine, for assistance in some of the experiments.

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THE EFFECTS OF ANTERIOR INFARCTION COMPLICATED BY BUNDLE BRANCH BLOCK UPON THE FORM OF THE QRS COMPLEX OF THE CANINE ELECTROCARDIOGRAM

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IN MAN the characteristic changes in the form of the ventricular complex usually produced by myocardial infarction are often greatly modified or absent when one of the two main subdivisions of the His bundle is blocked. When the conduction defect is on the left side it is rarely possible to diagnose infarction with certainty by means of either limb leads or precordial leads. Block on the right side usually prevents the occurrence of characteristic signs of anterior infarction in the standard limb leads, but not in the precordial leads. Such data as are available suggest that, as a rule, it does not seriously obscure the diganostic signs of posterior infarction, which ordinarily appear in Leads II and III.

Because the number of cases in which both bundle branch block and infarction were known to be present is relatively small, it seemed expedient to undertake an experimental study of the electrocardiographic changes produced by this combination of lesions. The methods employed in our experiments were those used in the electrocardiographic studies of infarction carried out by Wilson, Hill, and Johnston.[1]

Dogs of large or medium size were used. The heart was exposed, the right or left branch of the His bundle was cut in the usual way, and in most of the experiments the anterior descending coronary artery was ligated in its mid-portion. The chest was then carefully restored. These surgical procedures were carried out under aseptic conditions. After a period of seven to forty days, when the animal had recovered completely from the operation, the electrocardiographic observations were made. The standard limb leads and unipolar precordial leads were taken with the chest intact. Then the thorax was opened by splitting the sternum, and the anterior surface of the heart was explored by means of unipolar direct leads.

The standard limb leads of nine dogs are reproduced in Fig. 1. In the first three animals (57, 58, and 61) the right branch of the His bundle

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was cut, but there was no gross infarction, either because the anterior descending coronary artery was not ligated or because the attempt to occlude it was unsuccessful. The electrocardiograms of these animals are of the kind ordinarily seen in canine right branch block. Below these curves are three sets from animals (59, 62, and 66) with both right branch block and anterior infarction. It will be noted that no changes characteristic of infarction appeared in the ventricular complexes of the limb leads. In dogs with normal intraventricular conduction, infarcts similar in size and location to those induced in these experiments usually give rise to large Q deflections in Lead I.

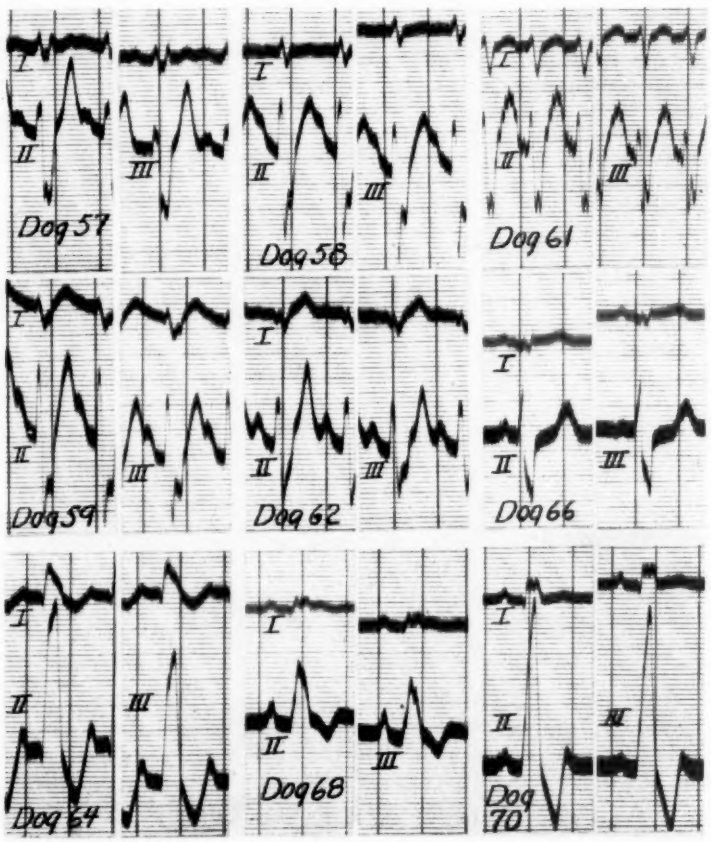

Fig. 1.—Standard limb leads with simultaneous Lead I. Upper row—three dogs with right bundle branch block. Middle row—three dogs with both right branch block and anterior infarction. Lower row—Dog 64 had left bundle branch block; Dogs 68 and 70 had left branch block and anterior infarction.

The first set of curves of the last row (Fig. 1) are from an animal (64) with left branch block only, and the second and third sets are from animals (68 and 70) with both left branch block and anterior infarction. Here also the limb leads display no changes in the ventricular complex that suggest the presence of infarcted cardiac muscle.

The precordial curves were obtained by moving the exploring electrode across the precordium in the same way as when taking comparable human curves. The exploration was begun at a point to the right of the right margin of the sternum, and was extended to a point well to the left of the apex beat. The electrode consisted of a stiff copper wire, insulated by enamel except at the ends. One end was sharpened and was brought into contact with the subcutaneous tissues by making a small slit in the skin. The enamel was removed from the opposite end for a

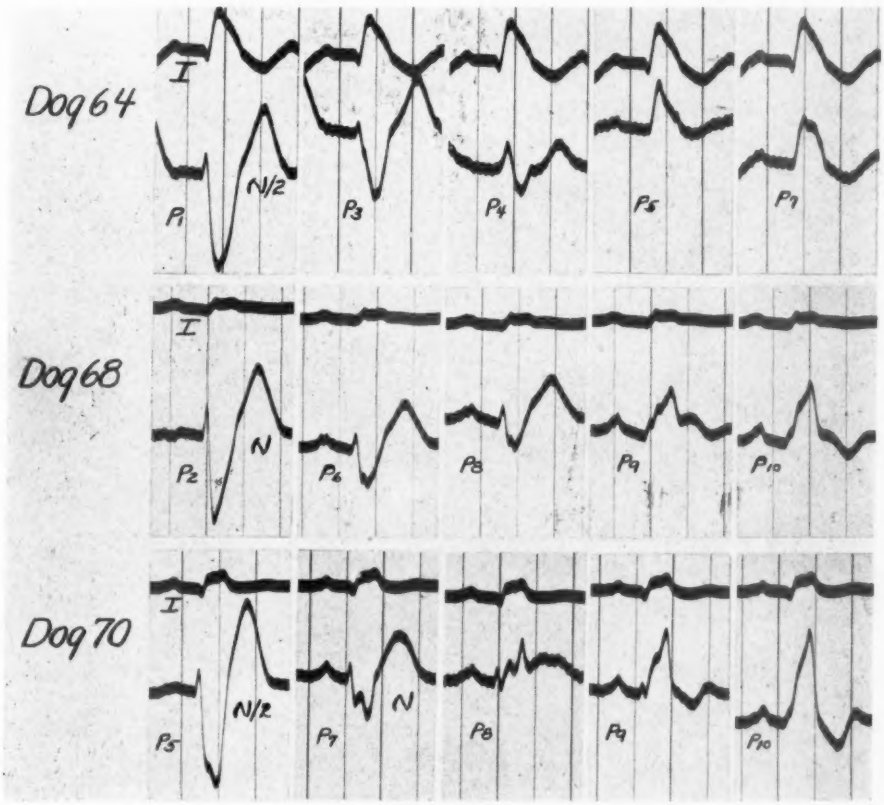

Fig. 2.—Unipolar precordial leads. Dog 64 had left bundle branch block. Dogs 68 and 70 had left branch block and anterior infarction.

short distance so that the electrode could be connected to the appropriate lead wire. The precordial points explored were arranged along a broken line running across the precordium from right to left, and were approximately 2 cm. apart. The exploring electrode used in taking both the precordial and the direct leads was paired with a central terminal connected through resistances of 5,000 ohms to electrodes on the two forelegs and on the right hind leg. Leads taken in this way are referred to as "unipolar leads."

The unipolar precordial curves obtained in uncomplicated canine bundle branch block are strikingly similar to those that represent human bundle branch block, apart from the length of the QRS interval, which is considerably shorter in the dog than in man. In left branch block there are no other easily detectable differences. In leads from the right side of the precordium the QRS complex consists of a small initial R component, followed by a deep, broad S deflection. In leads from the left side of the precordium it is monophasic, and is represented by a broad-topped, slurred, notched, or bifid R wave (Fig. 2, Dog 64).

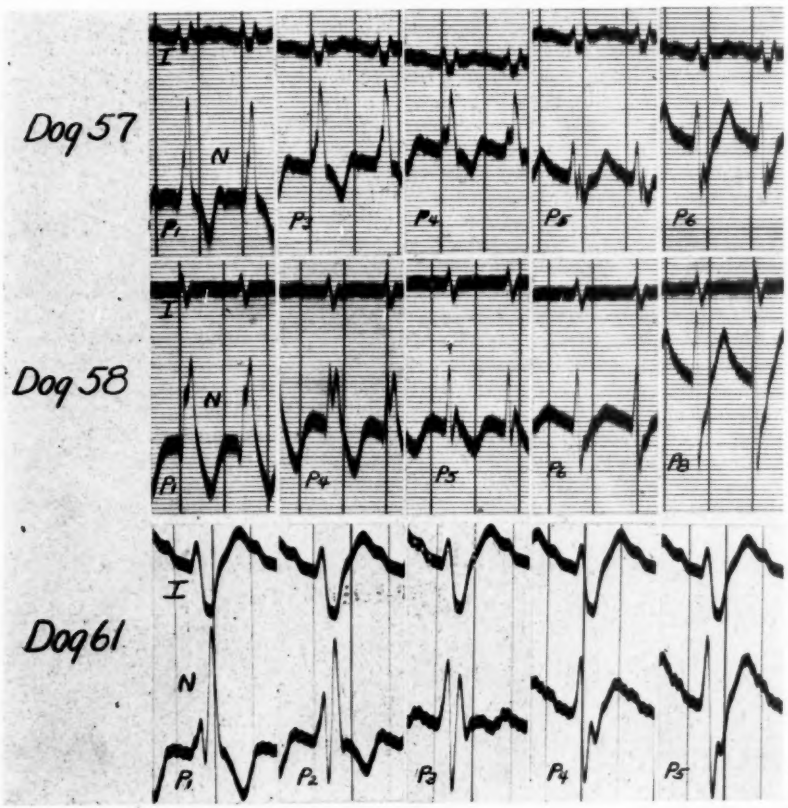

Fig. 3.—Unipolar precordial leads from three dogs with right bundle branch block.

In right bundle branch block the leads from the right side of the precordium display a large R or R′ deflection which reaches its apex late in the QRS interval. In some instances this deflection is preceded by an initial downward movement, or Q wave (Fig. 3, Dogs 57 and 58), in which case its ascending limb is usually slurred or notched. In other instances (Fig. 3, Dog 61) it is preceded by a small initial R component, followed by a conspicuous dip, and notching of its upstroke is absent or less conspicuous. As the exploring electrode is shifted to

the left this initial R rapidly increases in height and is transformed into a slender, tall, upward deflection which reaches its apex early in the QRS interval. At the same time, the downward movement which follows it increases in depth, and the late secondary R′ component rapidly diminishes in size until it is represented by a notch on a deep, broad S wave. Precordial electrocardiograms of this second type are very much more common in human right branch block than those of the first type. In leads from the left side of the precordium the QRS complex always has essentially the same form, and consists of a narrow R deflection, sometimes preceded by a small Q, and a broad, slurred, or notched S wave. The voltage of the slender R is usually smaller in comparison with that of the broad S in the curves of the dog than in those of man.

When right branch block is complicated by anterior infarction (Fig. 4), leads from the right side of the precordium display a tall, late R wave, preceded by a deep Q deflection. As the exploring electrode is shifted to the left the R wave rapidly diminishes in size, and disappears or is submerged below the isoelectric level. In leads from the left side of the precordium the early, slender R wave which is present when there is no infarction is absent, submerged, or greatly reduced in height. In other words, the characteristic changes in the QRS complex consist in the development of large Q or QS deflections in leads from points overlying the infarct, and large Q waves, followed by late R waves, in leads from the right side of the precordium. In one of our experiments (Dog 66) the QRS complex of the lead taken farthest to the right (P_{10}, Fig. 4) showed no changes suggesting infarction. When left bundle branch block is present, anterior infarction gives rise to no characteristic modification of the QRS complex in precordial leads (Fig. 2, Dogs 68 and 70).

Intelligent interpretation of the ventricular complexes of unipolar precordial leads must be based upon the relations between the components of these complexes and the corresponding deflections of unipolar leads from the anterior surface of the exposed heart. In the animals with bundle branch block but no infarction, there was a very close resemblance between the ventricular complexes of the leads from the right side of the precordium and the ventricular complexes of the leads from the exposed surface of the right ventricle, and likewise between the complexes of the leads from the left side of the precordium and those of the leads from the exposed surface of the left ventricle. Curves depicting these relations in right branch block without infarction (Dog 58) and in left branch block without infarction (Dog 64) have recently been published in a general article on the precordial electrocardiogram.[2] We shall, therefore, confine the present discussion to experiments in which bundle branch block was complicated by infarction. In order to conserve space and to avoid needless repetition, comments and discussion necessary to the understanding and interpreta-

tion of the observations made in the experiments described here in detail have not been relegated to a separate section, but are interspersed with the presentation of the relevant data.

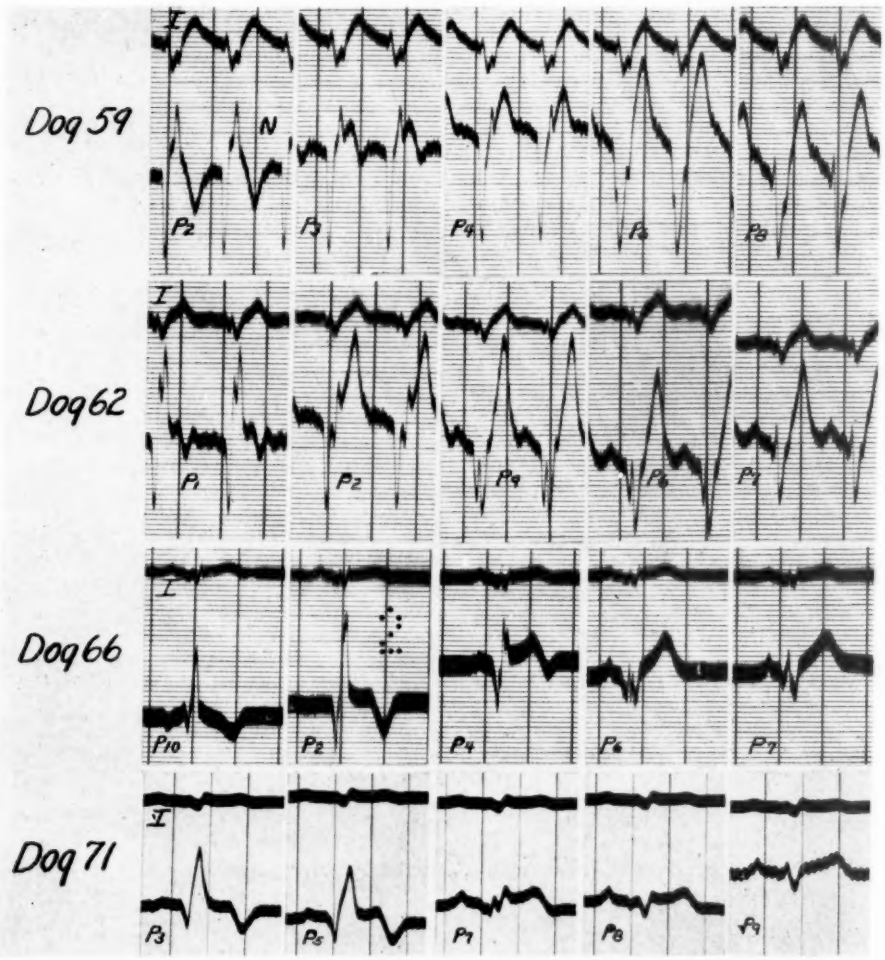

Fig. 4.—Unipolar precordial leads from four dogs with right bundle branch block and anterior myocardial infarction.

Dog 66.—The locations of the points on the epicardial surface explored in this experiment are shown on the outline drawing of the heart reproduced in Fig. 5. The points indicated by numbers not followed by a letter were studied with a soft-tipped electrode consisting of a small glass tube connected to a short length of soft rubber tubing cut on a bias at its lower end. The glass tube was stoppered with salted kaolin, and filled with 10 per cent copper chloride solution in which a long coil of copper wire was immersed. The short rubber extension was packed with cotton wool saturated with isotonic saline. When this electrode

was pressed lightly against the epicardium, no injury or only minimal injury to the underlying muscle resulted. The points marked by numbers followed by the letter *s* were explored with the sharp electrode used in taking precordial leads. This electrode was employed to distinguish dead from living muscle. When it was brought into contact with the former there were no injury effects in the curve obtained, but the latter yielded prominent RS-T displacement or completely monophasic ventricular complexes. The points designated by numbers followed by the letter *c* are those at which the sharp electrode was thrust through the ventricular wall in order to record the potential variations of the ventricular cavity. The first of the precordial curves reproduced (P_{10} of Fig. 6) was obtained from a point approximately 4.5 cm. to the right of the midsternal line. The ventricular complexes which it displays are

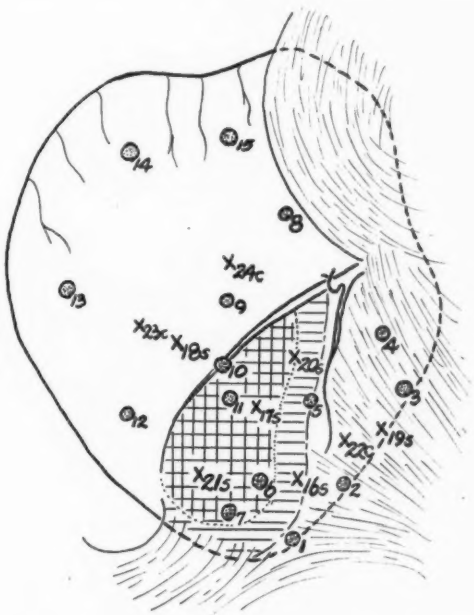

Fig. 5.—Dog 66. Outline drawing of anterior surface of exposed heart. Points explored with soft-tipped electrode indicated by stippled circles. Points explored with sharp electrode indicated by *X*; records taken from the surface are lettered *s*, and from the ventricular cavity are lettered *c*.

strikingly similar in outline to those of the direct leads from points *8, 12, 13, 14,* and *15,* which were all on the right ventricle. Since the deflections of all these leads are similar, only one, that from point *14,* is reproduced (Fig. 6). In these tracings the first QRS component is a small R wave, followed by a dip which reaches or barely crosses the isoelectric level. The second component is a tall R′ deflection which reaches its apex late in the QRS interval and displays a shoulder on its ascending limb. In right bundle branch block the muscle of the free wall of the right ventricle is not activated until late in the QRS

interval. During the earlier phases of this interval it contains no boundary between active and resting muscle and produces no electromotive forces. So long as this is the case, the potential of its outer surface is practically identical with that of the neighboring part of the ventricular cavity. It is not surprising, therefore, that in the tracings obtained from the ventricular cavity by thrusting a sharp electrode through the wall of the right ventricle at points *23c* and *24c* (Fig. 6), the earliest phases of the QRS complex are similar to the corresponding phases of the QRS complexes of the epicardial leads. The small, early R wave of these leads is faithfully reproduced in the internal leads.

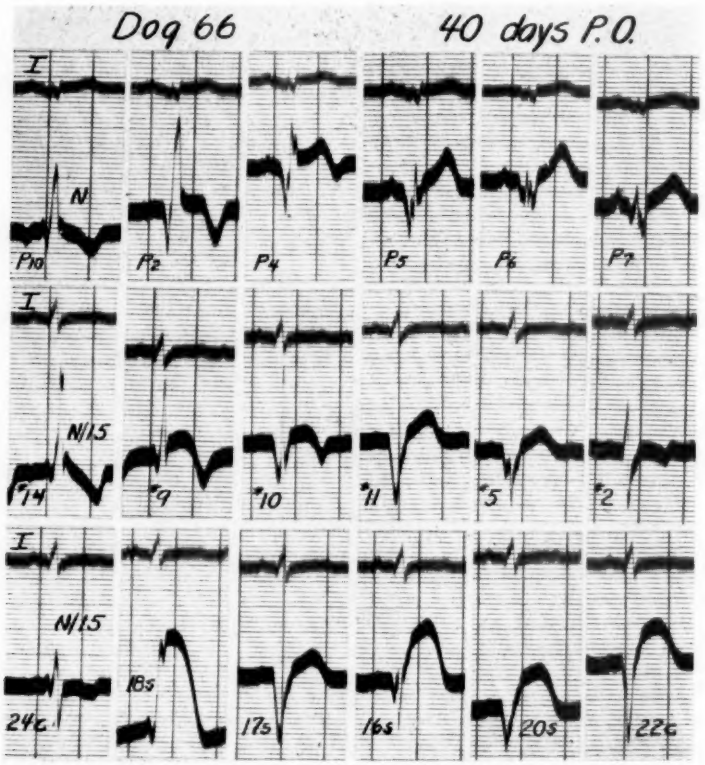

Fig. 6.—Dog 66. Right bundle branch block and anterior infarction. Upper row—unipolar precordial leads. Middle row—epicardial leads obtained with soft-tipped electrode. Lower row—epicardial and cavity leads obtained with sharp electrode.

The second R peak of the latter, which represents the maximum positivity attained by the ventricular cavity, evidently corresponds to the shoulder or thickening of the ascending limb of the late R′ deflection of the external leads. During the latter part of the QRS interval the epicardial surface is positive and the ventricular cavity negative, indicating that there is then a large electromotive force in the right ventricular wall. This force is responsible for that part of the late

R′ wave of the epicardial leads which follows the shoulder on its ascending limb.

It will be noted that the ventricular complexes of the lead from point *18s*, in which there is almost complete fusion of QRS and T due to the injury to the subepicardial muscle induced by the sharp electrode, do not differ, as regards those QRS components which precede the peak of the late R′ deflection, from the complexes obtained when a soft electrode was used. It has been pointed out in a previous publication[3] that injury to the subepicardial muscle can have no effect upon the form of the ventricular complex up to the instant at which the excitatory process arrives at the injured region. Since the subepicardial muscle of the right ventricle is not activated in right bundle branch block until the peak of R′ is inscribed, injury to this muscle has no effect on the earlier phases of the QRS complex.

The ventricular complexes of the direct leads from points *9* and *10* (Fig. 6) display a slender R or R′ deflection which reaches its apex late in the QRS interval and is preceded by a conspicuous downward movement. The RS-T segment is convex upward and the end of the T wave sharply inverted. The QRS complexes of the lead from point *9* begin with a small initial R, which is missing in the lead from point *10*. Both of these points were close to the interventricular sulcus, but their exact relation to the anterior attachment of the septum is not known. It is often difficult to interpret the deflections of leads of this kind because of uncertainty as to whether the recorded potential variations of the epicardial surface were more closely related to those of the right or to those of the left ventricular cavity. In the case of the lead from point *10*, it appears probable that the early phases of the QRS complex were determined by the potential variations of the cavity of the left ventricle; in the case of the lead from point *9*, the corresponding phases of QRS are apparently due in part to the potential variations of the cavity of the right ventricle. The ventricular complexes of these leads display many of the features often seen in leads from the marginal parts of an infarct which involves the left ventricular wall and is more extensive on its endocardial than on its epicardial side.

Unipolar epicardial leads from transmural infarcts that contain no appreciable amount of muscle capable of responding to the excitatory process yield ventricular complexes almost identical with those of leads from the adjacent part of the ventricular cavity. It will be noted that the ventricular complexes of the lead from point *11* are similar to those of lead *22c*, which represent the potential variations of the cavity of the left ventricle, and that the ventricular complexes of lead *17s*, in which a sharp exploring electrode was employed, are of the same kind. Since the last shows no RS-T displacement, it is evident that the muscle in the neighborhood of points *11* and *17s* was dead, or at least not responding to the cardiac impulse. The leads from points *6* and *7* and

the lead from point *21s* gave complexes practically identical in outline with those of the leads from points *11* and *17s*.

Unipolar epicardial leads from parts of left ventricular infarcts that contain appreciable amounts of muscle which responds to the cardiac impulse and lies in the outer layers of the ventricular wall yield QRS complexes characterized by large QS deflections notched by submerged R waves, or by abnormally large Q components followed by R waves of subnormal voltage. Infarction of the outer layers of muscle without involvement of the inner layers should theoretically reduce the size of the R component without producing abnormal Q waves, but this appears to be rare or nonexistent. In the present instance, notched QS deflections occurred in the lead from point *5*. The leads from points *16s* and *20s* show definite RS-T displacement, indicating the presence of living muscle. In the former the small R component is preceded by a broad Q deflection, which suggests that the subendocardial muscle was involved. Points *5*, *16s*, and *20s* evidently lie near the left margin of the infarct. The ventricular complexes of precordial leads P_4, P_5, and P_6 were evidently dominated by the potential variations of the infarcted region; they show many of the features of the ventricular complexes of the direct leads from points *5* and *11*.

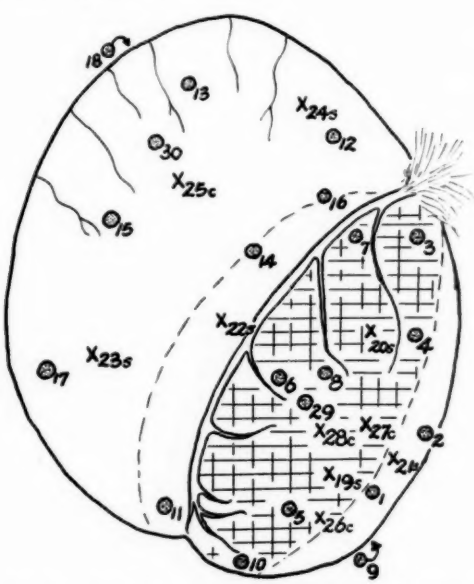

Fig. 7.—Dog. 71. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

The direct leads from points *1*, *2* (see Fig. 6), *3*, and *4*, which were still farther to the left and in a zone supplied by a branch of the anterior descending artery which came off above the ligature, present ventricular complexes of the normal form. The lead from point *19s* shows conspicuous RS-T displacement, indicating that the muscle in

this zone was responding. All of these points evidently lie to the left of the infarcted region. The ventricular complexes of precordial lead P_7 apparently represent a mixture of the potential variations at the surface of the infarct and those at the surface of the uninvolved wall to the left of it.

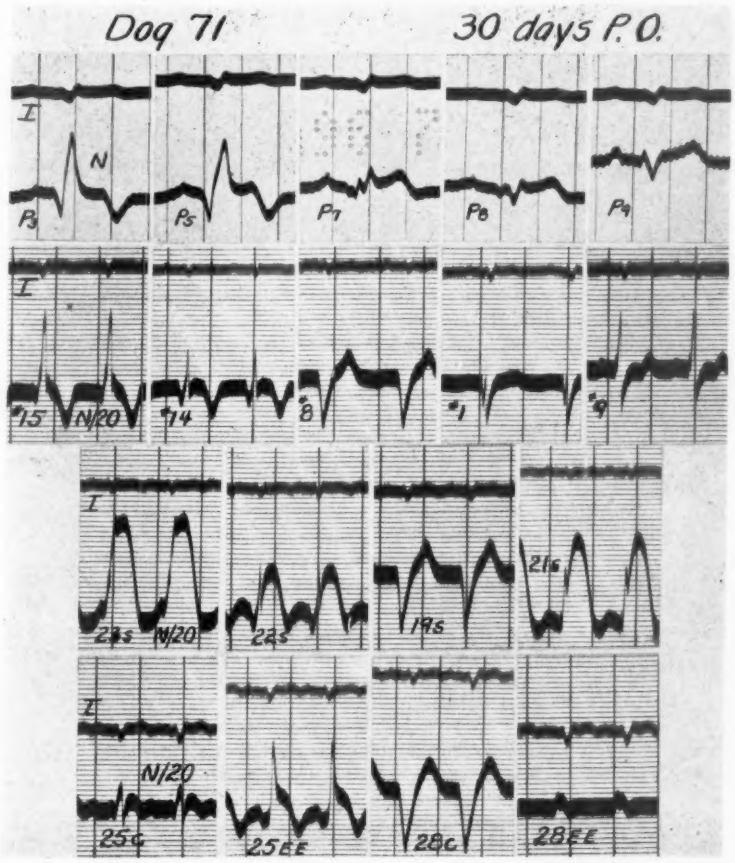

Fig. 8.—Dog 71. Right bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—epicardial leads obtained with soft-tipped electrode. Third row—epicardial leads obtained with sharp electrode. Fourth row—leads from ventricular cavities and transmural leads (marked *EE*).

Dog 71.—The locations of the epicardial points explored in this experiment are indicated in Fig. 7, and characteristic examples of the curves obtained are reproduced in Fig. 8. The ventricular complexes of the leads from points *11, 13, 17,* and *18* are similar in every respect to those of the lead from point *15* (Fig. 8). All of these points were on the free wall of the right ventricle. In the leads from points *12, 14,* and *16,* the QRS complex consists of a prominent Q wave, followed by a late R deflection which is very small in the lead from the last of these points; the T wave is sharply inverted. Points *14* and *16* were close

to the interventricular sulcus, and it is possible that point *12* was much less distant from it than is indicated in Fig. 7. The curves obtained with the sharp electrode at points *22s*, *23s*, and *24s* show pronounced RS-T displacement; in the first the earliest phases of the QRS complex are like those of the lead from point *11*, and in the others they are like those of the lead from point *15* and like those of the lead from the cavity of the right ventricle at point *25c*. It will be observed that the potential variations of the different parts of the epicardial surface and of the cavity of the right ventricle in this experiment were strikingly similar to those recorded in the case of Dog 66.

In the leads from points *3*, *4*, *5*, *6*, *7*, *8*, and *10*, the ventricular complexes consist of large, unnotched QS deflections, followed by positive T waves, and do not differ from those of the leads from the left ventricular cavity at points *27c* and *28c*, or from those of the leads from points *19s* and *20s*. The absence of RS-T displacement in these last two leads indicates that the muscle in contact with the sharp electrode was not responding to the cardiac impulse. The leads from points *1* and *2* present notched QS deflections, and the lead from point *21s* shows conspicuous RS-T displacement. These points were evidently close to the left margin of the infarct. In the lead from point *9*, the ventricular complexes are of the normal form. In this experiment transmural leads were taken in order to measure the variations in the voltage across the ventricular walls during the QRS interval. In these leads a sharp electrode thrust through the wall into the ventricular cavity was paired with a soft electrode on the epicardial surface. The galvanometer connections were made in such a way that relative positivity of the epicardial electrode produced an upward deflection in the finished record. In the lead marked *25 EE*, the soft electrode was on the free wall of the right ventricle at point *30*, and the sharp electrode was in the right ventricular cavity near point *25c*. The QRS complexes of this lead begin with a broad, shallow Q deflection, indicating slight relative negativity of the external surface. Late in the QRS interval there is a tall, sharp R deflection due to activation of the muscle between the two electrodes which made the epicardial surface strongly positive with respect to the ventricular cavity. The RS-T displacement is upward, and probably represents injury due to the pressure exerted by the outer electrode. The lead marked *28EE* was obtained by pairing a soft electrode at point *29* on the outer surface of the infarct with an internal electrode thrust through the ventricular wall at point *28c*. In this case the QRS deflections are very small. Since the infarcted muscle was not responding to the cardiac impulse, this part of the ventricular wall developed no electromotive force between its inner and outer surfaces. The small potential difference recorded is ascribed to electromotive forces generated at a considerable distance from the two electrodes and bearing nearly the same spatial relation to both of them.

The precordial leads in this experiment are clearly diagnostic of right branch block complicated by anterior infarction. There are abnormally large Q waves, followed by late R deflections in the leads from the right side of the precordium, and in the leads from the left side of the precordium the early R component ordinarily present in uncomplicated right branch block is absent, submerged, or abnormally small. It is also clear that the potential variations of the precordial points and the potential variations of the nearest parts of the ventricular surface were closely related. The resemblance between the precordial curves and the ventricular complexes of the direct leads is, however, somewhat less striking than in the case of Dog 66. Since large QS deflections occurred in the direct leads from a large part of the anterior surface of the left ventricle, it is surprising that they were not more faithfully reproduced in the leads from the left side of the precordium. If the precordium had been more completely explored, QS deflections larger than those present in precordial lead P_8 might have been obtained.

Dog 59.—The locations of the epicardial points investigated in this experiment are indicated in Fig. 9, and characteristic examples of the curves obtained are reproduced in Fig. 10. The leads from points *3, 4, 8,* and *19* on the free wall of the right ventricle display a late R wave, preceded by small preliminary deflections consisting of an initial downward movement followed by a positive deflection of about the same size. This second preliminary deflection notches the ascending limb of R. Similar preliminary deflections are present in the leads from points *13s* and *25s,* which were taken with the sharp electrode, but in the last the downward movement is preceded by a small positive peak. In the lead from the ventricular cavity at point *24c* this positive peak is well developed, but it is not followed by a conspicuous depression. The principal R wave of this internal lead corresponds in time to the notch or shoulder on the upstroke of the R wave of the epicardial leads. The difference between the earliest potential variations of the right ventricular cavity and those of the epicardial surface of the free wall of the right ventricle was not, therefore, as great as the first glance at the tracings suggests.

In the leads from points *2, 12s, 17s,* and *21s,* all close to the interventricular sulcus, the ventricular complex consists of a conspicuously notched QS deflection of moderate depth, followed by a positive T wave. Since the sharp electrode produced no upward RS-T displacement in the last three of these leads, it is apparent that most of the muscle in this zone was dead and that the infarct extended across the interventricular sulcus.

In the leads from points *1, 7,* and *18,* the QRS complex consists of a deep, notched or slurred QS deflection. At points *10s, 14s,* and *23s,* the sharp electrode yielded deep Q or QS deflections, followed by moderate upward displacement of the RS-T junction, indicating that some

of the subepicardial muscle, but not all of the subendocardial muscle at these points, was responding to the cardiac impulse. The leads from points *5, 6, 9, 11s,* and *20s* indicate that the corresponding parts of the ventricular wall were normal. At point *22s* the sharp electrode yielded a curve which shows no upward RS-T displacement, and in which the QRS complex is unnotched and similar to that of the lead from the cavity of the left ventricle near point *23c*, indicating that in this region the infarct was transmural.

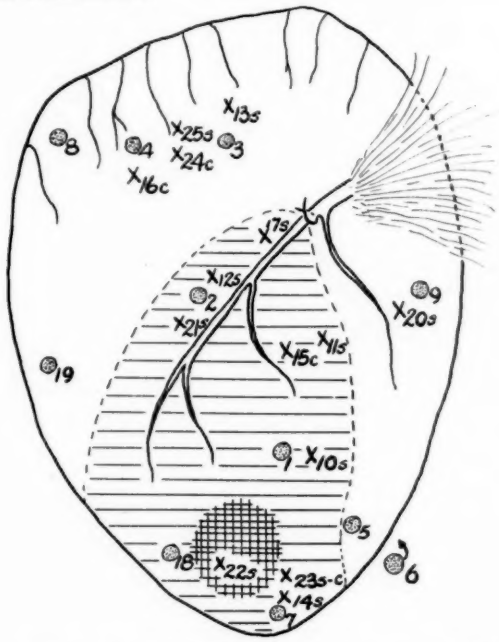

Fig. 9.—Dog 59. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

There is a close relation between the form of the ventricular complexes of the leads from the left side of the precordium and those of the direct leads from the epicardial surface of the left ventricle. In the leads from the right side of the precordium the initial Q deflection is much larger in comparison with the late R wave than in the two experiments previously described (Dogs 66 and 71). As regards the presence of these large Q components, the ventricular complexes of these leads are unlike those of the direct leads from the epicardial surface of the free wall of the right ventricle. The same phenomenon is seen in the semidirect leads (*SD* in Fig. 10) which were taken from a pad of gauze soaked in isotonic saline solution and laid upon the exposed heart. This pad was approximately 1 cm. thick, and the exploring electrode was moved across it step by step in a base-apex direction, so that the earliest leads (*1* and *2*) were from parts of the pad lying on the right ventricle. The ventricular complexes of these leads resemble those of

the corresponding precordial leads in general contour. It is apparent that in this experiment the potential variations of the surface of the infarct were unusually well transmitted to the right side of the precordium and to the right side of the gauze pad. The reason may lie in the extension of the infarct to the right of the interventricular sulcus. The same phenomenon occurred in the case of Dog 62, but in this instance the animal died prematurely, so that a satisfactory number of direct leads could not be taken. In this experiment, also, there was spotty infarction of the part of the right ventricular wall adjacent to the sep-

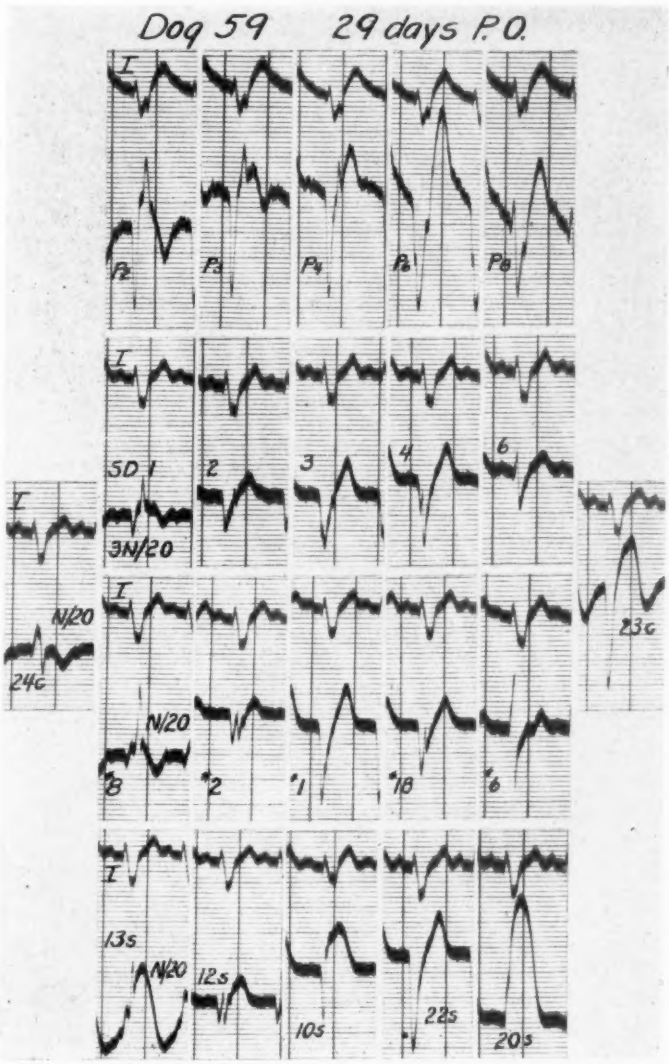

Fig. 10.—Dog 59. Right bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—semidirect leads from saline soaked gauze pad laid upon exposed heart. Third row—epicardial leads with soft-tipped electrode. Fourth row—epicardial leads with sharp electrode. Tracings labeled *24c* and *23c* are leads from the right and left ventricular cavities, respectively.

tum. It should be noted that, during the earliest parts of the QRS interval, the potential variations of the surface of the infaret were much larger than those of the right ventricular surface, whereas later in this interval this situation no longer existed. This explains why the potential variations of the right side of the precordium were at first like those of the infareted region, and later like those of the anterior surface of the right ventricle.

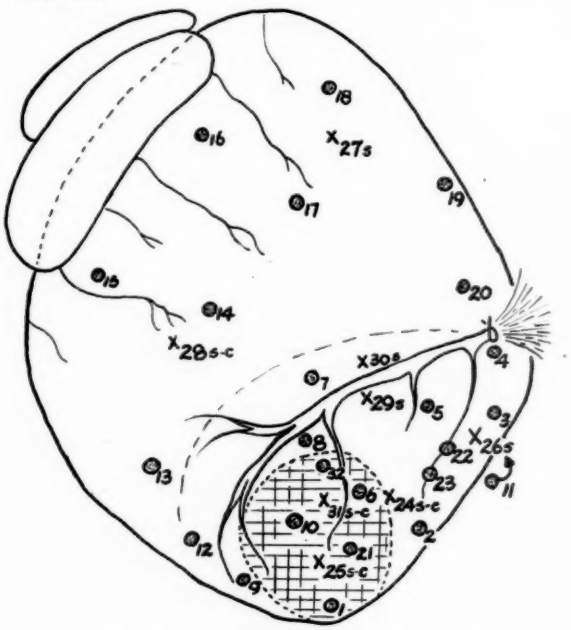

Fig. 11.—Dog 70. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

Dog 70.—The locations of the epicardial points explored in this experiment are shown in Fig. 11, and some of the tracings obtained are reproduced in Fig. 12. In the leads from the free wall of the right ventricle at points *13, 14, 15, 16, 18,* and *19,* the QRS complex consists of a slender initial R deflection, followed by a deep, broad, and slurred S wave. The T wave is upright. The ventricular complex is of the same form in the leads from points *7, 12,* and *20,* except that in the last there is a mere trace of the initial R wave, and also in the leads from points *4, 5, 8,* and *9,* which were equally close to the anterior descending artery, but on the opposite side of it. In the dog it is the rule that the time of activation of points just below this artery is not much affected by section of either the right or left bundle branch. At points *27s, 28s, 29s,* and *30s,* the sharp electrode induced pronounced upward RS-T displacement.

In the lead from point *2* the QRS complex consists of a tall, late R wave which displays conspicuous slurring of the first part of its ascend-

ing limb. This limb is notched near its onset by a small summit. The T waves are inverted. Ventricular complexes of essentially the same kind are present in the leads from points *11*, *22*, and *23*. In the lead from point *3* the peak of the R wave is earlier, but in this lead, also, this deflection is preceded by a small summit. There are a large S and a

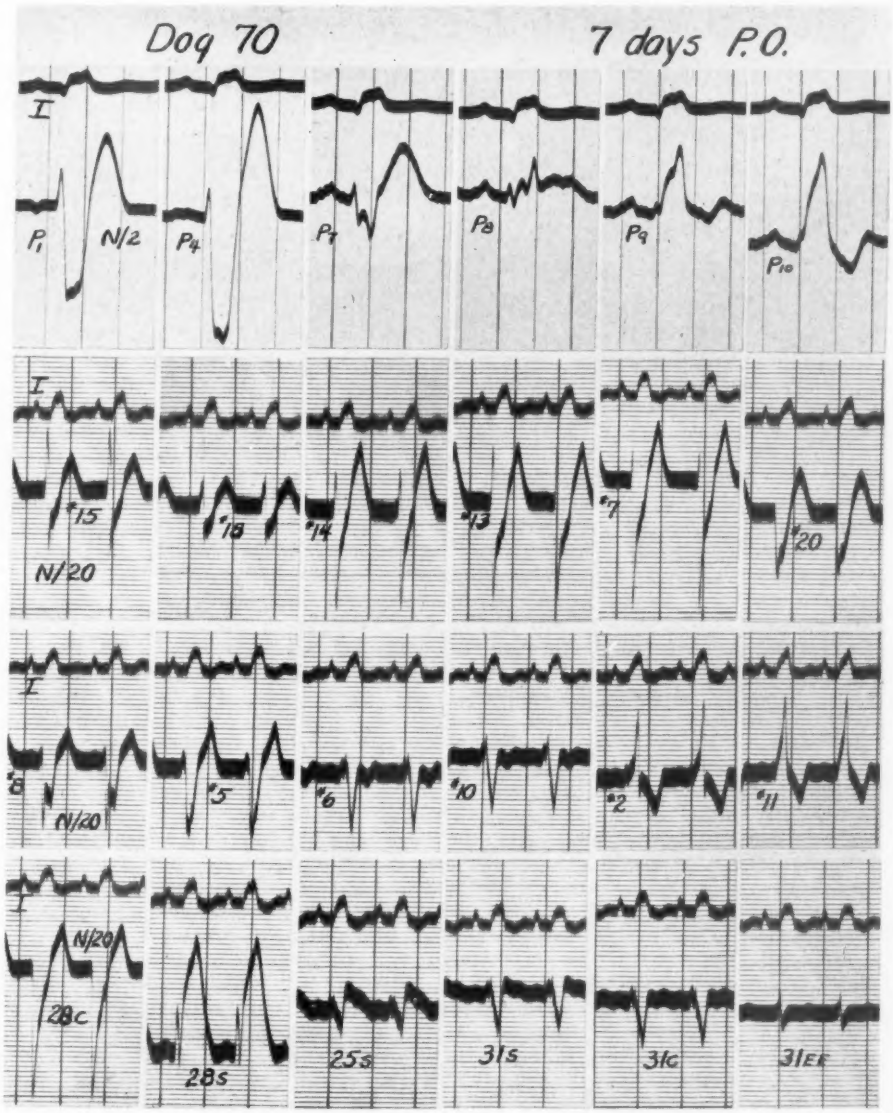

Fig. 12.—Dog 70. Left bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—epicardial leads from right ventricle with soft-tipped electrode. Third row—epicardial leads from left ventricle with soft-tipped electrode. Fourth row—epicardial and cavity leads with sharp electrode. Transmural lead labeled *EE*.

positive T wave. The sharp electrode produced a large upward displacement of the RS-T junction in the lead from point *26s*.

In the leads from points *1, 6, 10,* and *21,* the ventricular complexes are of essentially the same form as in the lead from the ventricular cavity near point *24c*. The QRS deflections consist of two sharp, but very low, summits, followed by a deep S deflection, and the T wave is diphasic or inverted. The sharp electrode yielded moderate upward RS-T displacement at point *24s,* slight displacement at point *25s,* and very slight displacement at point *31s*. In all of these leads the initial QRS deflections are similar to those of the lead from the ventricular cavity. It is apparent that a considerable part of the ventricular wall in this region was infarcted.

A transmural lead from the ventricular cavity near point *31c* to the epicardial surface at point *32* (marked *31EE* in Fig. 12) shows very small deflections, indicating that the ventricular wall in this neighborhood was producing no appreciable electromotive force and was not responding to the cardiac impulse. It should be pointed out that in the leads from the infarcted region (points *1, 6, 10,* and *21*) the large downstroke which begins at the peak of R is not nearly as steep as it is in the leads from uninjured parts of the ventricular walls. The absence of a very abrupt downstroke or true intrinsic deflection distinguishes the QRS complex of these leads from those of all the other leads taken with the soft electrode, with the possible exception of the lead from point *5* (see Fig. 12).

The ventricular complexes of the leads from the right side of the precordium (P_1 to P_7, inclusive) are strikingly similar in general outline to those of the direct leads from the free wall of the right ventricle and the zones on either side of the anterior descending coronary artery. The ventricular complexes of the leads from the left side of the precordium (P_9 and P_{10}) resemble those of the direct leads from the uninfarcted anterolateral wall of the left ventricle. None of the precordial leads displays ventricular complexes like those of the direct leads from the surface of the infarct. The reason probably lies in the relatively small size of the region within which a large part of the ventricular muscle was killed. But even if this region had been much larger, and the potential variations over its surface had been more faithfully transmitted to the precordium, it is unlikely that modifications of the precordial curves diagnostic of infarction would have resulted. As has been clearly shown, the potential variations at the epicardial surface of a transmural infarct are always practically identical with those of the adjacent parts of the ventricular cavity. When the left branch of the His bundle conducts normally, the cavity of the left ventricle is negative throughout the QRS interval, and leads from the surface of trans-

mural left ventricular infarcts yield deep QS deflections which clearly indicate the nature of the lesion. If the infarct is anterior and not too small, similar deflections occur in suitable precordial leads. When left branch block is present, however, the cavity of the left ventricle is positive at the beginning of systole because of the electromotive force generated by the spread of the cardiac impulse through the septum from right to left. In this case, leads from the outer surface of a transmural infarct of the left ventricular wall display QRS complexes that consist of an R deflection of variable size, followed by an S wave of like or greater voltage. Such deflections in precordial leads are not sufficiently distinctive to have much diagnostic value. If they occur in leads from the extreme left side of the precordium, which ordinarily yield QRS complexes consisting of a single component, a broad, slurred, notched, or bifid R wave, they may justifiably lead to the suspicion that an infarct is present, but cannot furnish reliable evidence of the existence of such a lesion. The recognition of infarction of the free wall of the left ventricle in the presence of left bundle branch block on the basis of modifications of the QRS complex is, therefore, extremely difficult.

SUMMARY

In dogs, myocardial infarcts induced by ligating the anterior descending coronary artery in its middle third do not usually modify the QRS complexes of the standard limb leads in a characteristic manner when bundle branch block is present.

When such infarcts are complicated by right bundle branch block, the QRS complexes of unipolar leads from the right side of the precordium display a large, initial Q deflection, followed by an R wave which attains its summit late in the long QRS interval. The first component is due to potential variations transmitted from the epicardial surface of the infarcted region, and the second to potential variations transmitted from the epicardial surface of the free wall of the right ventricle. Leads from that part of the precordium overlying the infarct present large, broad QS deflections, often conspicuously slurred or notched.

When left branch block is present, infarction of the kind in question does not give rise to characteristic changes in the QRS complexes of the precordial leads because the potential of the left ventricular cavity and, therefore, of the epicardial surface of the infarcted region is positive during the earliest part of the QRS interval. In direct leads from the epicardial surface of the infarct, the QRS complex consists of an initial R deflection of variable size, followed by an S component of like or greater voltage. In the case of very large lesions, QRS complexes of this kind probably occur in leads from precordial points overlying the part of the left ventricular wall which is affected, but cannot be considered reliable evidence of infarction.

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CORONARY OCCLUSION, CORONARY INSUFFICIENCY, AND ANGINA PECTORIS

A Clinical and Post-Mortem Study

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THE frequency of disease of the coronary arteries[1, 2] has lent great impetus in recent years to the study of this disease, both clinically and pathologically.[3-5] It is now known to be the most important disease of all, considering all age groups. In large part this is due to the increase in the span of life,[1] enabling many more persons to reach the age at which coronary artery disease is prevalent. The subject is of critical importance today, when a large army is being formed, for it has been shown that coronary artery disease is common among military personnel over the age of 40 years.[6] It is, therefore, essential that correct terminology be used in discussing coronary disease, but considerable confusion exists at the present time with respect to the use of the terms "coronary occlusion" and "coronary insufficiency."

Coronary artery occlusion means sudden, complete obstruction of a coronary artery. The symptoms and signs associated with the attack include severe and prolonged substernal pain, shock, impairment of the first heart sound, gallop rhythm, occasionally a pericardial rub, a fall in blood pressure, fever, leucocytosis, and a rapid sedimentation rate. Acute coronary insufficiency indicates necrosis or infarction of the myocardium without complete closure of a coronary artery. This concept of acute coronary insufficiency has been firmly established as a specific entity by the work of many authors, both in Germany [7-11] and in this country.[6, 12-16] It has been demonstrated conclusively that pain and necrosis or infarction of the myocardium may be produced by severe or prolonged diminution in coronary flow in the absence of coronary occlusion.

Some writers[17, 18] have been prompted to discard the term "coronary occlusion" on the assumption that it is impossible clinically to differentiate coronary occlusion with infarction from coronary insufficiency with necrosis or infarction of the heart muscle. They thus relegate the term "coronary occlusion" to the post-mortem room. We do not agree with this point of view, for, in our experience, coronary occlusion with infarction presents characteristic clinical and electrocardiographic changes which are almost always distinguishable from those produced

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TABLE I

DIFFERENTIATION OF ANGINA PECTORIS, CORONARY INSUFFICIENCY, AND CORONARY OCCLUSION

	ANGINA PECTORIS	ACUTE CORONARY INSUFFICIENCY	CORONARY OCCLUSION
PHYSIOLOGY	Ischemia, transitory (inadeqate coronary circulation)	Ischemia, severe or prolonged (inadequate coronary circulation)	Total cessation of coronary flow in obstructed artery
PATHOLOGY	1. Coronary arteries: sclerosis and narrowing 2. Myocardium: no acute changes	Variable degree of sclerosis or normal Necrosis: small, diffuse areas, subendocardial, papillary muscle No pericarditis No mural thrombosis	Sclerosis. Occlusion by thrombus or intimal hemorrhage Infarction—large, confluent, endo-, myo-, and pericardial Pericarditis common Mural thrombosis with embolization common
PREDISPOSING FACTORS	Coronary sclerosis Hypertension Aortic stenosis and insufficiency Graves' disease Anemia Syphilitic ostial stenosis	Coronary sclerosis Hypertension Aortic stenosis Cardiac enlargement Anemia Syphilitic ostial stenosis	Coronary sclerosis Hypertension
PRECIPITATING FACTORS	Effort Emotion Cold Eating Trauma Reflex from other viscera Tobacco Insulin Adrenalin	1. Similar to angina pectoris 2. Acute conditions with anoxemia Hemorrhage Shock or fall in blood pressure Sudden rise in blood pressure Tachycardia Heart failure Infections Trauma Operation, anesthesia	None Operation?
PAIN	Temporary Relieved by nitroglycerin	Variable, often absent	Prolonged Not relieved by nitroglycerin
CIRCULATION			
1. Shock	None	May be present	Common
2. Blood pressure	No change or rise	Falls	Falls
3. Heart sounds	No change	May be poor	Embryocardia, gallop, pericardial rub
4. Arrhythmias	None	Occasional	Common
5. Heart failure	None	May be present	Common
6. Fever	Absent	Frequently absent	Present
7. Sedimentation rate	Normal	Frequently normal	Abnormal
ECG	Usually no change Evanescent RS-T depressions	RS-T depressions and T-wave changes for several days or weeks No Q waves or RS-T elevation	RS-T elevation Q waves Leads I and III reciprocal Progressive pattern, often permanent
DURATION OF INCAPACITY	Minutes to few hours	Several hours or weeks	Prolonged
PROGNOSIS	Good	Usually full recovery Occasionally fatal Often depends upon precipitating factor	Usually permanent symptoms Often fatal

by infarction caused by coronary insufficiency.[13-16] Although both conditions occasionally result in similar clinical entities, coronary occlusion usually presents a well-defined syndrome which is readily distinguished from coronary insufficiency, and both conditions differ in their causal relationship to severe exertion and trauma. It is thus obvious that a correct terminology of coronary disease is essential, and that it is important to distinguish coronary occlusion clearly from coronary insufficiency.

A major difference between coronary occlusion and coronary insufficiency is in the mode of onset (Table I). The start of coronary oc-

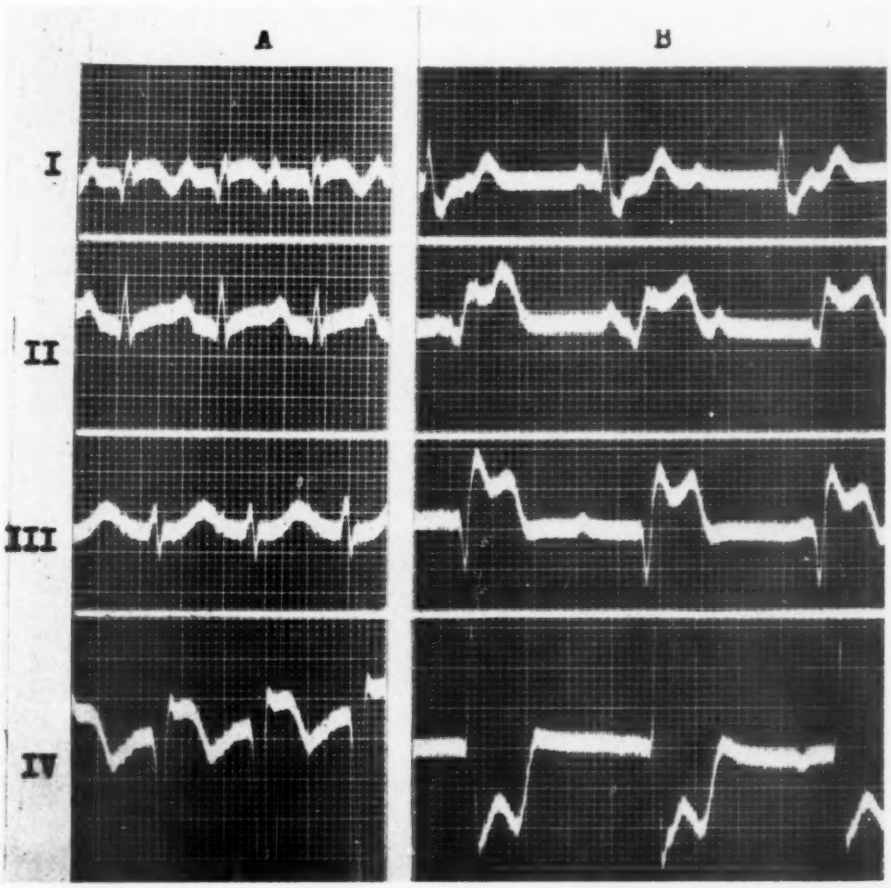

Fig. 1A.—Case 44. K. F., a man, 35 years of age. The electrocardiogram is characteristic of acute coronary occlusion with anterior wall infarction; it shows deep Q waves, elevation of the RS-T segments, and inversion of the T waves in Leads I and IV. There is a reciprocal relationship of the RS-T and T waves in Leads I and III. Autopsy—acute occlusion of anterior descending branch of left coronary artery, with infarction of anterior surface of left ventricle.

Fig. 1B.—Case 39. M. H., a man, 68 years of age. The electrocardiogram is characteristic of acute coronary occlusion with posterior wall infarction; it shows deep Q waves and elevation of the RS-T segments in Leads II and III, depression of RS-T in Leads I and IV, and inversion of T_4. There are also complete heart block and intraventricular block as a result of infarction of the posterior portion of the septum. Autopsy—acute occlusion of the right coronary artery with infarction of the posterior aspect of the left ventricle and interventricular septum.

clusion is independent of outside influences, such as effort and excitement, and actually is most common during rest or sleep.[19] It is the end result of the progressive atherosclerotic process in a coronary artery, and the exact time of occurrence is a fortuitous event. Coronary insufficiency, on the contrary, is due to a sudden inadequacy of coronary blood flow, produced by a number of factors. Thus, unusual effort and emotion increase the work of the heart; acute hemorrhage, shock, tachycardia, heart failure, surgical operations, and aortic valve disease diminish the amount of blood flow through the coronary arteries. If either increased cardiac work or diminished coronary blood flow develops in the presence of coronary artery disease, the myocardium may become ischemic and, if the precipitating factor persists, necrosis of the heart muscle may ensue. Occasionally no discernible cause of

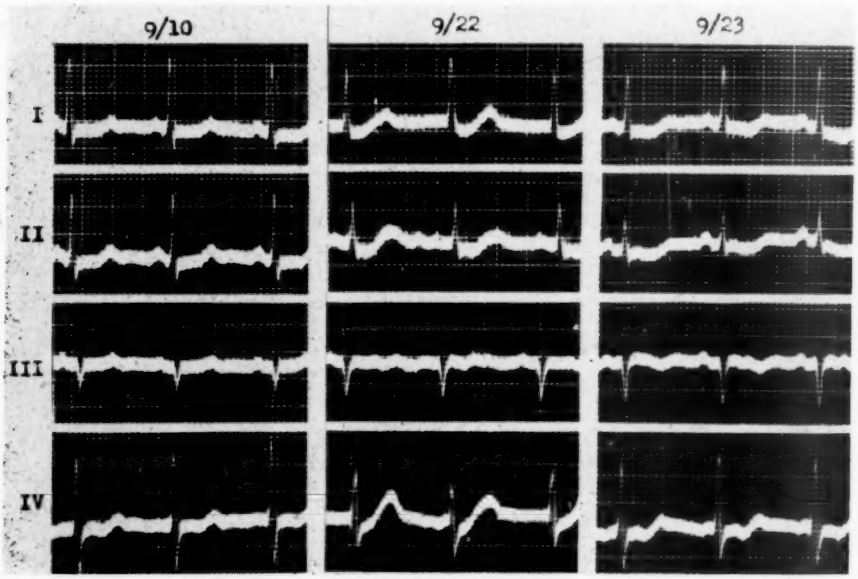

Fig. 2.—L. H., 494959, a woman, 55 years old, with hypertension and carcinoma of the stomach. Five days after subtotal gastrectomy she developed dyspnea, cyanosis, and signs of congestive and peripheral failure, and died five days afterwards. The preoperative electrocardiogram (9/10) showed left axis deviation and slight RS-T depression in Leads I and II. The electrocardiogram after the attack (9/22) showed increased depression of RS-T in these leads and depression in Lead IV. The next day (9/23) the T waves were diphasic in Leads I, II, and IV, and inverted in Lead III. The occurrence of RS-T depression and T-wave inversion, in the absence of RS-T elevation or deep Q waves, pointed to coronary insufficiency rather than to coronary occlusion. Post-mortem examination revealed a large embolus in the right pulmonary artery. There was no obstruction in the coronary arteries.

the coronary insufficiency is present. Unlike coronary occlusion, pain may be a minor symptom in coronary insufficiency, and sometimes is obscured entirely by the condition causing the ischemia, for example, shock or a surgical operation.[15] Even when present, the pain is often transitory. In other cases status anginosus may be present. In general, when no precipitating factor of an attack is apparent, the differential

diagnosis of coronary occlusion and insufficiency may depend on the electrocardiogram.

The electrocardiogram is considered characteristic of acute coronary occlusion when elevation of the RS-T segment and a deep Q wave are present in one or more leads (Fig. 1), with progressive change from RS-T elevation to T-wave inversion in serial records.

In acute coronary insufficiency the typical electrocardiographic changes consist of RS-T depression and T-wave inversion in two or more leads (Fig. 2). RS-T elevation and deep Q waves are absent. Unlike that in coronary occlusion, the electrocardiogram returns to its original configuration in several days or weeks.

MATERIAL

We have attempted to evaluate the clinical and electrocardiographic differences between coronary occlusion and coronary insufficiency by studying the 100 consecutive cases in which the diagnosis of coronary occlusion had been made or suspected by the physicians on the wards and which were examined post mortem. After death we reviewed the cases clinically and electrocardiographically and divided them as follows:

Cases 1 to 49, with electrocardiograms considered characteristic of coronary occlusion because of the presence of Q waves and RS-T elevation, progressing into T-wave inversion. Therefore, it was predicted that coronary occlusion would be found at autopsy in these cases.

Cases 50 to 55, with bundle branch block appearing for the first time. The sudden occurrence of bundle branch block, in association with a typical history in a person of middle age, suggested the diagnosis of coronary occlusion.

Cases 56 to 60, with electrocardiograms characteristic of coronary insufficiency, i.e., RS-T depressions and T-wave inversion, progressing or retrogressing under observation. Because of the absence of Q waves and RS-T elevation we predicted that myocardial necrosis due to coronary insufficiency, without occlusion, would be found at autopsy.

Cases 61 to 62, presenting the typical electrocardiographic pattern of pulmonary embolism, i.e., large S_1 and Q_3, and T_4 inverted.

Cases 63 to 100, a nondescript clinical group with nonspecific electrocardiographic changes. Because of the absence of any characteristic or progressive electrocardiographic pattern, such as those found in the preceding groups, neither coronary occlusion nor coronary insufficiency could be diagnosed clinically. This group included a very heterogenous series of cases. In many, careful consideration of the history and clinical observations, as well as of the electrocardiogram, disclosed the fact that the preliminary diagnosis of coronary occlusion should have been discarded early. Thus, a number of cases were not cardiac at all; these included bronchopneumonia, cerebral accident, nephritis, and peritonitis. Among the cardiac cases were acute and chronic cor pulmonale, heart failure, and coronary occlusion and insufficiency. In many of these cases the electrocardiograms could not be used for several reasons. For example, sometimes only one or two records were taken at long intervals. In other cases the administration of digitalis confused the interpretation. In a number of cases the electrocardiogram previous to the attack was markedly abnormal, with large Q waves, RS-T deviations, T-wave

TABLE II

ELECTROCARDIOGRAPHIC AND AUTOPSY OBSERVATIONS IN 100 CONSECUTIVE CASES OF SUSPECTED CORONARY OCCLUSION

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	AUTOPSY				REMARKS
					OCCLUSION	INFARCT	NECROSIS	PERI-CARDITIS	
A. Electrocardiogram Considered Characteristic of Coronary Occlusion									
1. J. R.	443599	60	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed	L.C.*	+	-	-	
2. A. S.	431656	60	M	Q_4, RT_4 elevated, auricular fibrillation	L.A.D.†	+	-	-	
3. E. M.	444867	61	F	$Q_{2,3}$, $RT_{2,3}$ elevated	L.C.	+	-	+	
4. S. W.	450219	59	M	Q_4, RT_2 elevated, $T_{1,2,3}$ inverted	R.C.‡	-	+	-	
5. I. S.	425318	45	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $T_{2,3}$ inverted	R.C.	+	-	-	
6. M. O.	457838	74	M	$Q_{1,2,3}$, $RT_{1,2,4}$ elevated	L.C.	+	-	+	
7. E. H.	463375	55	F	$Q_{2,3}$, $RT_{2,3,4}$ elevated	R.C.	+	-	-	
8. I. L.	458033	57	M	Q_4, $RT_{1,2,3,4}$ elevated	L.A.D.	+	-	+	
9. L. C.	460046	44	M	$Q_{3,4}$, $RT_{1,2}$ depressed, $T_{1,2,3}$ inverted	L.A.D. R.C.	+	-	-	
10. S. L.	452172	74	M	Q_4, RT_4 elevated, 2_1 inverted	L.A.D.	+	-	-	
11. M. S.	465417	51	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $T_{2,3}$ inverted	R.C.	+	+	+	
12. L. C.	454753	43	M	Q_4, RT_4 elevated T_4 inverted	L.A.D.	+	-	-	
13. H. D.	446681	43	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	-	-	
14. J. S.	443387	47	M	$Q_{2,3}$, $T_{2,3}$ inverted	L.A.D.	+	-	-	
15. H. K.	466751	60	M	Q_3, RT_3 elevated, $RT_{1,2,4}$ depressed	R.C.	+	-	+	
16. M. R.	438083	54	M	Q_4, $RT_{1,2,3,4}$ elevated	L.A.D.	+	-	+	
17. L. S.	438516	42	M	$Q_{2,3}$, $RT_{2,3}$ elevated, RT_1 depressed	L.A.D.	+	-	+	
18. Z. W.	462881	54	M	$Q_{2,3,4}$, RT_4 elevated	R.C.	-	+	+	
19. J. D.	449072	55	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	-	+	-	
20. E. P.	452870	82	F	Q_4, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	-	-	
21. M. H.	429651	72	M	$Q_{2,3,4}$, $RT_{1,2,3,4}$ elevated	L.A.D.	+	+	+	
22. A. K.	430289	59	M	$Q_{2,3}$, $T_{2,3}$ inverted	R.C.	-	+	-	
23. J. M.	387038	65	M	$Q_{2,3}$, RT_3 elevated, $RT_{1,4}$ depressed	R.C.	+	-	-	
24. D. B.	398067	56	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	-	-	
25. B. V.	448363	50	F	Q_4, $T_{1,4}$ inverted	L.A.D.	+	-	-	

*L.C.—Left circumflex coronary artery.
†L.A.D.—Left anterior descending coronary.
‡R.C.—Right coronary artery.

26. A. L.	446600	50	M	$Q_{1,2,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	−	−	
27. H. B.	406061	62	M	$Q_{2,3,4}$, $T_{2,3}$ inverted	R.C.	+	−	−	
28. O. L.	407587	63	M	$Q_{1,2}$, $RT_{3,4}$ elevated, $T_{1,2,4}$ inverted	L.A.D.	+	+	−	
29. J. S.	407390	53	M	$Q_{1,4}$, $RT_{1,4}$ elevated, RT_3 depressed	L.A.D.	+	−	+	
30. P. S.	398088	55	F	$Q_{1,4}$, $RT_{1,4}$ elevated, RT_3 depressed	L.A.D.	+	−	+	
31. J. W.	413699	63	M	Q_4, $RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	−	−	
32. J. K.	385381	56	M	Q_4, T_1 inverted	L.A.D.	+	−	−	
33. N. D.	392407	60	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed	L.C. R.C.	+	−	+	
34. R. T.	397182	51	F	$RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	−	−	
35. J. L.	399108	67	F	$Q_{2,3}$, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed	R.C.	+	−	−	
36. H. H.	472077	65	M	$Q_{1,2,4}$, RT_1 elevated, T_1 inverted	L.C.	+	−	−	
37. M. R.	476291	55	M	$Q_{2,3}$, $RT_{2,4}$ elevated, RT_4 depressed, $T_{2,3}$ inverted	R.C.	+	−	+	
38. C. S.	477281	75	M	Q_4, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	−	+	
39. M. H.	477591	68	M	$Q_{2,3}$, $RT_{2,3}$ elevated, RT_1 depressed	R.C. L.C.	+	−	+	
40. W. F.	477687	56	F	$Q_{1,4}$, $RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	−	+	
41. D. K.	486395	47	F	$Q_{2,3}$, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed, $T_{2,3}$ inverted	R.C.	+	−	+	
42. M. F.	379066	57	M	$Q_{2,3}$, RT_3 elevated, $RT_{1,4}$ depressed, $T_{2,3}$ inverted	L.C. R.C.	+	−	−	
43. S. B.	387028	52	M	Q_3, $RT_{1,2,4}$ depressed, $T_{1,2,3,4}$ inverted	L.A.D. R.C.	+	−	−	
44. K. F.	436371	35	M	$Q_{1,2,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed, $T_{1,4}$ inverted	L.A.D.	+	−	−	
45. M. G.	384952	46	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	−	−	
46. S. G.	404600	67	M	$Q_{2,3}$, $RT_{2,3}$ elevated, RT_4 depressed, $T_{2,3}$ inverted	L.C.	+	−	+	
47. L. D.	414717	62	M	$Q_{1,2,3,4}$, $RT_{1,2,4}$ elevated	L.A.D.	+	−	−	
48. S. I.	428761	54	M	RT_4 elevated, $T_{1,2,4}$ inverted	−	−	+	−	Postoperative coronary insufficiency
49. J. K.	483543	59	M	Q_3, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed, T_1 inverted	−	−	−	−	Postoperative shock

TABLE II—CONT'D

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	AUTOPSY				REMARKS
					OCCLUSION	INFARCT	NECROSIS	PERI-CARDITIS	
B. Electrocardiogram Not Characteristic of Coronary Occlusion									
a. *Bundle Branch Block*									
50. M. K.	453380	65	M	Left B.B.B. Ventricular tachycardia	L.A.D.	−	+	−	
51. D. F.	383531	75	M	Left B.B.B. Prolonged P-R	R.C.	+	−	−	
52. T. B.	395287	58	M	Left B.B.B.	L.A.D.	+	−	−	
53. W. F.	444679	51	M	Left B.B.B. Complete A-V block	L.A.D. L.C.	+	−	+	
54. D. D.	387259	52	F	Left B.B.B.	R.C.	+	−	−	
55. S. F.	381691	46	M	Right B.B.B.	L.A.D. R.C., L.D.	+	−	−	
b. *Characteristic of Coronary Insufficiency*									
56. A. H.	436060	60	F	$RT_{1,2}$ depressed, $T_{1,2}$ inverted	−	−	−	−	Coronary insufficiency
57. S. B.	413383	55	F	$T_{2,3,4}$ inverted	−	−	−	−	Coronary insufficiency
58. M. R.	457972	60	M	$T_{1,2,3,4}$ inverted	−	−	−	−	Coronary insufficiency
59. J. C.	434920	68	M	$T_{1,2,3,4}$ inverted	−	+	−	−	Coronary insufficiency Pneumonia
60. B. W.	442487	64	M	RT_1 depressed, T_1 inverted	−	+	−	−	Coronary insufficiency
c. *Characteristic of Pulmonary Embolism*									
61. R. P.	384075	84	F	Q_3, RT_3 elevated, S_1	−	−	+	−	Pulmonary embolism
62. R. S.	385365	70	F	Q_3, RT_3 elevated, S_1	−	−	−	−	Pulmonary embolism
d. *Nonspecific*									
63. S. H.	402869	50	M	T_1 inverted	L.A.D.	+	−	−	
64. J. L.	381256	62	M	$T_{1,2,3}$ inverted	L.C.	+	−	−	
65. P. B.	386384	67	M	$T_{1,2,3}$ inverted	R.C.	+	−	−	
66. A. L.	458297	69	M	$T_{1,2,3,4}$ inverted, $RT_{1,2,3,4}$ depressed	L.A.D.	+	−	−	
67. A. V.	415936	61	M	T_1 inverted	R.C.	+	−	−	
68. A. G.	404952	52	M	$T_{1,4}$ inverted	R.C.	−	−	−	
69. M. H.	453889	70	M	$Q_{2,3}$, $T_{1,2,3}$ inverted (present before attack)	R.C.	−	+	−	

70. C. B.	434487	68	M	$T_{1,2,3}$ inverted	L.A.D.	–	–	–	
71. A. K.	445549	74	M	Q_4, $RT_{1,2}$ depressed	L.A.D.	+	–	–	
72. B. B.	376989	73	F	$RT_{1,2,3}$ depressed, $T_{1,2,3}$ inverted	L.A.D. R.C.	+	–	–	
73. M. E.	390038	36	F	Q_3, $T_{2,3,4}$ inverted (present before attack)	R.C.	+	–	–	
74. E. A.	455567	48	F	Hypertensive pattern	R.C.	+	–	–	
75. E. B.	422603	65	M	Hypertensive pattern	–	–	+	–	Coronary insufficiency
76. M. W.	421978	71	M	Q_3, RT_3 elevated, $T_{1,2,3}$ inverted (prior to attack)	–	+	–	–	Coronary insufficiency
77. A. K.	438614	68	M	Right B.B.B	–	–	+	–	Coronary insufficiency
78. I. R.	432200	67	M	$T_{2,3,4}$ inverted	–	–	–	–	Acute cor pulmonale
79. J. S.	467157	57	M	$T_{2,3}$ inverted	–	–	–	–	Acute cor pulmonale
80. A. G.	447269	45	M	Hypertensive pattern	–	–	+	–	Pulmonary embolism
81. A. E.	459042	73	M	Hypertensive pattern	–	–	–	–	Pulmonary embolism
82. W. S.	392658	60	M	Hypertensive pattern	–	–	–	–	Pulmonary embolism
83. S. S.	447331	69	M	Hypertensive pattern	–	–	+	–	Pulmonary embolism
84. L. S.	445536	59	M	$T_{1,2,3,4}$ inverted	–	–	–	–	Chronic cor pulmonale, heart failure
85. B. F.	395731	52	F	$T_{1,2,3,4}$ inverted	–	–	+	–	Heart failure
86. S. P.	463069	62	M	Q_3, $T_{1,2}$ inverted (prior to attack)	–	–	–	–	Heart failure Bronchopneumonia
87. R. S.	456510	51	M	$Q_{2,3,4}$, $T_{1,2,3,4}$ inverted prior to attack)	–	–	–	–	Heart failure
88. S. B.	434527	74	M	$T_{1,2,3}$ inverted, Q_3 (prior to attack)	–	–	+	–	Heart failure
89. M. N.	474767	60	M	$RT_{1,2}$ depressed, $T_{1,2,3}$ inverted	–	–	–	–	Heart failure
90. E. B.	434121	77	M	Hypertensive pattern	–	–	–	–	Heart failure, pneumonia
91. J. B.	433469	62	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
92. L. S.	461830	70	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
93. J. A.	463891	45	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
94. M. R.	449478	85	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
95. N. P.	435696	47	M	$T_{2,3}$ inverted	–	–	–	–	Bronchopneumonia
96. A. H.	431847	71	M	Normal	–	–	–	–	Postoperative pneumonia
97. M. F.	447501	46	M	$T_{1,2,3}$ inverted	–	+	–	–	Pneumonia
98. M. K.	434044	48	M	$RT_{1,2}$ depressed, $T_{1,2,3,4}$ inverted	–	–	–	+	Chronic nephritis
99. C. H.	459753	68	F	$T_{2,3}$ inverted	–	–	–	–	Cerebral accident
100. L. L.	461925	66	M	T_1 low	–	–	–	–	Peritonitis

inversion, or bundle branch block. There were seven instances of "hypertensive" records, i.e., left axis deviation, high voltage QRS, and RS-T depression and T-wave inversion in Lead I. In view of the indiscriminate clinical diagnoses and electrocardiographic changes, which were stationary in this group of cases, it was considered best not to make any prediction concerning what would be found at autopsy. Actually, in the majority of cases coronary occlusion had not been considered seriously, even clinically.

After we had thus predicted what would be found post mortem, the coronary arteries were studied minutely by multiple cross sections at 2 to 3 mm. intervals.[4] Numerous microscopic sections of suspicious areas in the vessel, as well as in the myocardium, were also examined. The accuracy of this method and the number of coronary occlusions detected by it compare favorably with any other method described.

RESULTS

The electrocardiographic and post-mortem observations in each case are presented in Table II. The characteristic pattern of acute coronary occlusion, consisting of RS-T elevations and deep Q waves, was present in the electrocardiogram in Cases 1 to 49, inclusive, and, therefore, it was predicted that coronary occlusion would be found post mortem. This prediction proved to be true in forty-seven cases (Cases 1 to 47), i.e., 96 per cent of the cases. Not only did the electrocardiogram enable us to make the correct diagnosis of coronary artery occlusion in these forty-seven cases, but, in addition, it correctly indicated the site of infarction (anterior or posterior) in forty-five. When infarction involves the anterior surface of the left ventricle, the Q wave and RS-T elevation appear in Lead I and the chest leads; in posterior infarction, Leads II and III show these alterations. It is evident that, when the electrocardiogram presents RS-T elevation and Q waves, the diagnosis of coronary occlusion is practically certain. The two exceptions (Cases 48 and 49) proved to be instances of postoperative coronary insufficiency; necrosis of the myocardium was found only in Case 48; the other patient died within eighteen hours, possibly too soon for anatomic changes in the myocardium to have occurred. In the latter case (Case 49), a very profound state of shock suddenly developed several days after a cholecystectomy; there was no pain. In Case 48 an attack of precordial pain and shock followed prostatectomy; the bladder became severely infected and the patient's condition steadily declined. In both cases coronary sclerosis of moderate degree was found post mortem, but no evidence of recent or old occlusion. The presence of RS-T elevation in both these cases suggests that the myocardial ischemia was very severe. In summary, the electrocardiogram indicated coronary occlusion in forty-nine cases, and it was found post mortem in forty-seven.

Bundle branch block was present in six cases (Cases 50 to 55), with a typical history of coronary occlusion, and the latter was found post mortem in all. The sudden appearance of bundle branch block in association with an acute attack of pain or shock should make one suspect

acute coronary occlusion as the precipitating cause. On the other hand, it is frequently impossible to make a diagnosis of acute coronary occlusion in the presence of a bundle branch block pattern, for it may have existed prior to the attack and may not change as a result of it. The presence of RS-T elevation and Q waves may not be significant because they may be intrinsic in the bundle branch block pattern and bear no relation to the acute attack. However, the sudden onset of bundle branch block is suggestive of recent coronary occlusion.

In Cases 56 to 60 there was progressive RS-T depression or T-wave inversion, or both, i.e., changes typical of coronary insufficiency, and in all five cases this was confirmed at autopsy, which revealed coronary sclerosis without occlusion. Myocardial necrosis was present in three cases. The electrocardiographic changes occurred after operation.

In Cases 61 and 62 the electrocardiogram was typical of pulmonary embolism, and this was present in both at autopsy. Although the electrocardiographic pattern of pulmonary embolism may simulate coronary occlusion with posterior infarction, the proper diagnosis can usually be made if the diagnosis of pulmonary embolism is considered.

The remaining group (Cases 63 to 100), as we have seen, included a heterogeneous collection of noncardiac and cardiac cases and various clinical pictures, without any specific electrocardiographic pattern, which made it impossible to anticipate the post-mortem observations. We have already pointed out that in the majority of these cases the diagnosis of coronary occlusion should not have been entertained clinically. At autopsy the causes of death were various, including heart failure, nephritis, pneumonia, peritonitis, cor pulmonale, coronary insufficiency, and coronary occlusion.

COMMENT

Our results amply confirm the value of the term "coronary occlusion." Not only does it embrace a typical syndrome, well known to every physican, but it is associated with a characteristic, progressive, electrocardiographic pattern. The attack usually consists of severe, prolonged substernal pain, some degree of shock, a change in the heart sounds, e.g., gallop rhythm, a pericardial rub, a fall in blood pressure, and, frequently, heart failure. Fever, leucocytosis, and a rapid sedimentation time usually appear on the second or third days. The pain is not relieved by nitroglycerin. When RS-T elevation and deep Q waves are present in the electrocardiogram, it is almost certain that coronary occlusion exists; that is, it is present in 95 per cent of the cases. Such accuracy compares favorably with any diagnostic procedure in medicine. Yet, some authors have advocated discarding the term "coronary occlusion" merely because of the rare exceptions in which this clinical picture and electrocardiographic pattern are produced by infarction without occlusion. It should be emphasized that

coronary insufficiency itself, with or without infarction, also is associated in the majority of cases with a specific electrocardiographic pattern, namely, RS-T depression and abnormal T waves in two or more leads. Thus, with occasional exceptions, coronary occlusion and coronary insufficiency can be readily differentiated.

It is true, as we have found, that in some cases, coronary occlusion does not produce characteristic electrocardiographic changes, but that fact also does not militate against the use of the term; the same holds for some instances of coronary insufficiency. These cases are usually the ones in which the electrocardiogram was previously abnormal as a result of old coronary occlusion, bundle branch block, or marked enlargement of the heart, and the advent of another occlusion or of coronary insufficiency may not alter the electrocardiogram significantly, or may produce equivocal or nonspecific changes. In such cases the presence of a precipitating factor, such as effort, emotion, shock, operation, or hemorrhage, should make one suspect coronary insufficiency without occlusion. In the latter, the pain not infrequently is mild, a pericardial rub is absent, and heart failure usually is not severe. Fever, leucocytosis, and rapid sedimentation time are, as a rule, less marked than in coronary occlusion.

The term "acute coronary insufficiency," in the restricted sense described by us, has been employed and accepted for a number of years in the foreign literature, particularly in Germany.[7-11] The term then appeared in the American literature.[12-15] Its differentiation from coronary occlusion was clear. Therefore, the recent attempts to alter the meaning of the term to embrace all types of acute coronary disease, including coronary occlusion, seem to us confusing and without advantage. It would still be necessary to separate coronary insufficiency, in the narrower sense of myocardial infarction without occlusion, from coronary occlusion. We have shown that 95 per cent of cases can be divided into acute coronary occlusion and acute coronary insufficiency clinically and electrocardiographically, and it does not clarify the problem to discard both of these useful concepts because 5 per cent of the cases do not fall into either of the two groups. For similar reasons we object to another recent suggestion, namely, the use of the term "coronary failure" to designate all acute coronary seizures, whether due to occlusion or to insufficiency. This ambiguous term would merely add to the confusion, and is quite unnecessary.

The terms "coronary occlusion" and "coronary thrombosis" may be used interchangeably, but the former is preferred by us because it has been shown in recent years that the commonest mechanism of occlusion is intimal hemorrhage which may result in damage to the overlying endothelium and secondary thrombosis, or may even occlude the lumen without thrombosis.[3, 4]

The concept of angina pectoris has undergone considerable changes and discussion in recent years. It is now generally agreed that the attack represents a temporary insufficiency of the coronary flow, and it has been suggested, therefore, that the term "angina pectoris" be discarded, and one such as transitory coronary insufficiency be employed. Theoretically this is justified. However, the classical syndrome of angina pectoris, including the typical substernal pain and its radiation, its relation to effort, excitement, cold, and eating, and its relief by rest and nitroglycerin, is so characteristic and firmly established that it would seem advantageous to retain the term to connote one type of coronary insufficiency (Table I). It differs from the more severe forms of coronary insufficiency in that anatomic alterations do not occur in the cardiac muscle. Clinically, the attack of pain is usually of short duration. Shock is absent, the heart sounds and blood pressure are not significantly altered, and a pericardial rub and heart failure do not appear. Fever, leucocytosis, and an increase in the sedimentation rate are absent. Immediately after the attack the patient returns to his previous condition, that is, he may feel entirely well. The electrocardiogram is usually normal, but the changes characteristic of coronary insufficiency, that is, RS-T depression and T-wave abnormalities, may appear transiently during the attack. RS-T elevations and Q waves are not encountered.

CONCLUSION

The clinical, electrocardiographic, and post-mortem observations have been evaluated in one hundred consecutive cases in which the diagnosis of coronary occlusion had been entertained clinically.

Acute coronary disease should be divided into coronary occlusion and coronary insufficiency. Each of these is associated with a characteristic electrocardiographic pattern, and coronary occlusion usually presents a typical clinical picture.

Coronary occlusion is produced by obstruction of a coronary artery, and usually results in a confluent infarction extending from endocardium to pericardium. It is not related to external factors. The electrocardiogram typically presents deep Q waves and RS-T elevations, progressing into T-wave inversions which persist for a considerable period.

In forty-nine cases there was an electrocardiographic pattern which was regarded as characteristic of coronary occlusion, and the latter was found post mortem in forty-seven of these. In addition, the electrocardiogram correctly indicated whether the infarction was anterior or posterior.

Not every attack of coronary occlusion results in typical electrocardiographic alterations; this is true chiefly of multiple, fatal attacks.

The presence of a bundle branch block pattern in the electrocardiogram frequently makes the diagnosis of coronary occlusion uncertain.

Coronary insufficiency is usually precipitated by some factor which increases the work of the heart or reduces the coronary blood flow. The clinical picture is variable. The electrocardiogram shows RS-T depressions and T-wave inversions which last several hours or days. At autopsy, disseminated areas of necrosis are found in the subendocardial layer and papillary muscle.

The term "angina pectoris" is useful to indicate a transitory attack of chest pain which usually appears on effort, with transient or no acute electrocardiographic changes.

When the characteristic electrocardiographic pattern of coronary occlusion occurs, occlusion will be found at autopsy in 95 per cent of the cases.

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ELECTROCARDIOGRAPHIC CHANGES IN UREMIA ASSOCIATED WITH A HIGH CONCENTRATION OF SERUM POTASSIUM: REPORT OF THREE CASES

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IN A previous communication[1] we demonstrated that defects of intraventricular conduction developed in two cases of uremia in which the concentration of potassium in the serum was increased abnormally. Similar electrocardiographic changes had been noted by two groups of investigators in studies of experimental animals rendered toxemic by the injection of potassium salts or by the production of anuria.[2-4] In our experience and that of others, this electrocardiographic pattern in association with a marked increase of concentration of potassium in the serum has occurred rarely among uremic patients.[1, 5, 6] During the spring of 1943, for a period of six weeks, we observed a patient in different phases of uremia. Numerous electrocardiograms and estimations of the concentration of potassium in blood serum were made simultaneously on this patient. During the last few days of life the serum potassium increased rapidly and an intraventricular conduction defect developed. We therefore thought it desirable to publish in detail the clinical course, pathologic observations, studies of renal function and of the chemistry of the blood, and electrocardiographic changes in these three cases. Evidence will be presented that death was due to potassium intoxication.

REPORT OF CASES

CASE 1.—The patient, who was 18 years of age, was the son of a farmer. The family history was irrelevant to his present illness. The patient had contracted mumps and chicken pox in childhood. Tonsillectomy had been performed when he was 5 years of age. The present illness began March 3, 1936, five weeks before admission; it followed exposure to rain, when he became chilly and felt sick all over. Three days later, swelling of the face and ankles appeared and his physician found albumin in the urine. The patient was put to bed for two weeks, and during this period the edema subsided.

On admission, April 7, 1936, physical examination revealed the patient's height as 69 inches (175 cm.) and weight as 147½ pounds (67 kg.). There was edema of the eyelids, grade 1 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe edema), but no anemia; the tonsils had been removed previously. The cardio-

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TABLE I

DATA ON BLOOD AND RENAL FUNCTION OF PATIENT 1

DATE	WHOLE BLOOD			BLOOD SERUM						BLOOD PLASMA			RENAL FUNCTION AND ECG
	HGB., GM. IN 100 C.C.	UREA, MG. IN 100 C.C.	CREATININE, MG. IN 100 C.C.	PROTEIN, GM. IN 100 C.C.	ALBUMIN, GM. IN 100 C.C.	POTASSIUM		SODIUM, MG. IN 100 C.C.	SULFATE, MG. IN 100 C.C.	N.P.N., MG. IN 100 C.C.	CHLORIDE, MG. IN 100 C.C.	CO_2 COMBINING POWER, VOL. IN 100 C.C.	CHOLESTEROL, MG. IN 100 C.C.	
						MG. IN 100 C.C.	MEQ. IN 1,000 C.C.							
4/ 8/36	14.1	38							6.5					
4/10/36		26		4.2	1.7				5.6	29			340	Urea clearance 45 c.c. (maximum); sulfate clearance 12 c.c.
7/ 1/36	13.9	18		4.1	1.9				5.9	20				
10/ 3/39	4.3	220	13.2	4.9	1.9				21.0	157	615	28		ECG (2) A.M., P.M.
10/ 4/39														ECG
10/ 5/39		266	15.2			27.8	7.1						181	ECG
10/ 7/39														ECG
10/ 9/39		392	18.4			40.9	10.5	290						ECG*
10/10/39† 3:10 A.M.														

*Tracings taken and blood withdrawn for chemical studies nineteen hours before death.
†Patient died.

vascular system was objectively normal. However, the initial blood pressure was 150/80. The ocular fundi were normal. A roentgenogram of the chest was reported negative. Routine urinalyses, four in all, showed a specific gravity of 1.010 to 1.020, no reducing substances, and a large amount of albumin (grade 4); the sediment contained a moderate number of hyaline and granular casts, erythrocytes, and leucocytes. A high serum sulfate and a decrease in the clearance of both urea and sulfate indicated diminished renal function. During the patient's stay of six days in the hospital, the edema disappeared and his weight decreased 9¾ pounds (4.4 kg.). For studies of blood and renal function, see Table I. Our diagnosis was acute or subacute glomerulonephritis.

Two and a half months later a checkup revealed a healthy looking young man except for slight edema of the legs in the pretibial regions. The blood pressure was 130/85. Routine urinalysis still revealed a heavy precipitate of albumin, and, in the sediment, erythrocytes (grade 3).

The patient appeared to live comfortably for the next three years, working as a bookkeeper. Occasionally he noticed slight edema of the eyelids, but this would disappear after a night's rest. Two weeks before his return to the clinic a respiratory infection, accompanied by a dry cough and dyspnea, developed.

On the patient's third admission, Oct. 2, 1939, he appeared anemic and orthopneic; there was edema, grade 1, of the face and back and grade 2 of the legs. He weighed 155½ pounds (70.5 kg.). The heart was enlarged, measuring, on percussion, 3 | 12.5 cm. The heart rate was 106 per minute. There was an audible to-and-fro, leathery friction rub over the apex and base of the heart. There were moist râles over the bases of both lungs posteriorly and signs of consolidation in the right lower lobe. The blood pressure was 170/120. Examination of the ocular fundi showed edema of the disks of 3 and 2 diopters, scattered hemorrhages, and distinct narrowing of the retinal arterioles, i.e., signs of acute angiospastic retinitis. A roentgenogram of the thorax revealed evidence of bronchopneumonia in the lower part of the right lung. Routine urinalyses, six in all, revealed essentially the same results as on the previous visits, namely, a large amount of albumin, no reducing substances, and a sediment containing moderate numbers of hyaline and granular casts, erythrocytes, and leucocytes. There was a severe secondary anemia, with a concentration of hemoglobin of 4.3 Gm. per 100 c.c. of blood. The flocculation reaction for syphilis was negative; the concentration of urea and creatinine was very high, namely, 220 mg. and 13.2 mg. in 100 c.c. of blood, respectively, and there was a moderate reduction of the carbon dioxide combining power of the plasma (Table I). Thus, it was clear that the patient was suffering from chronic glomerulonephritis, severe renal insufficiency, uremia, anemia, hypertension, myocardial degeneration and failure, bronchopneumonia, and pericarditis.

Course in Hospital, Oct. 2 to 10, 1939.—The patient's temperature rose at times to 101° F. The volume of urine in twenty-four hours gradually decreased from 1,150 c.c. to between 100 and 300 c.c. during October 6, 7, and 8. A blood culture taken on October 3 failed to show any growth of organisms in forty-eight hours. On October 4 the patient was given a transfusion of 500 c.c. of blood, after which transitory pulmonary edema developed. The pericardial friction rub persisted

from the time of admission until death, on Oct. 10, 1939. Orthopnea, pain in the thorax, and apprehension were the patient's most troublesome symptoms. Electrocardiograms were taken on six occasions from October 3 to 9. The concentration of potassium in the serum was abnormally high, namely, 7.1 milliequivalents in 1,000 c.c. on October 5, but increased on October 9 to 10.5 milliequivalents in 1,000 c.c. (Table I). On this latter date the electrocardiograms showed great similarity to those of dogs poisoned by potassium (Fig. 1). On the following day, October 10, the patient died.

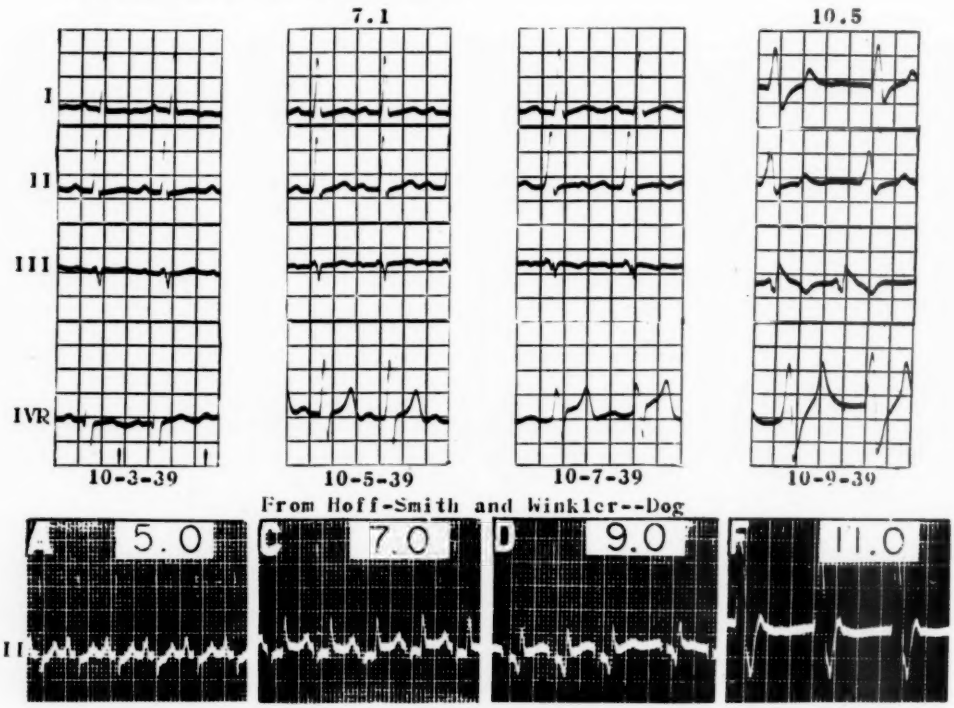

Fig. 1.—Electrocardiograms of Patient 1, which show progressive changes suggestive of po assium poisoning. In the first tracings (10/3/39) there is left axis deviation, with a shallow, diphasic T wave in Lead I. The second tracings (10/5/39) show an increase in the height of the T waves in all leads and a "peaked" appearance of the T wave in the chest lead. In the third tracings (10/7/39), delay of auriculoventricular conduction (P-R = 0.24 to 0.26 second) and widening of the QRS complex have made their appearance. In the last tracings (10/9/39), P waves cannot be identified, and there is a marked intraventricular conduction defect (QRS = 0.18 second). A few premature beats of probably ventricular origin are also present. Note similarity to tracings published by Hoff, Smith, and Winkler in their report on experimental intoxication with potassium (p. 608). Above the second and fourth tracings on Patient 1 are given the potassium content of the serum in milliequivalents as also noted, below, in the four tracings of the dog.

Necropsy.—There was moderate edema of the legs, and approximately 1,000 c.c. of clear fluid were present in the peritoneal cavity.

The heart weighed 740 grams. The epicardium was covered by fibrinous exudate. The walls of the left ventricle were thickened, and the ventricle was moderately dilated (Fig. 2*a*). Coronary sclerosis was graded 1.

There was chronic caseous tuberculosis in the lower part of the upper lobe of the right lung, with involvement of the hilar nodes. The lower lobe of the right lung was the seat of patchy bronchopneumonia.

The spleen weighed 230 grams, and was moderately congested. The liver weighed 2,245 grams, and was the seat of passive congestion of moderate degree. The lower end of the esophagus was covered by a pseudomembranous exudate. In the lower part of the ileum there were two small ulcers of Peyer's patches.

The right kidney weighed 140 grams. The surface was finely granular and the consisteney was moderately increased. The markings of the cut surface were indistinct. The cortex was 0.6 cm. in width, and the medulla, 1.5 cm. The left kidney weighed 147 grams and had the same appearance as the right.

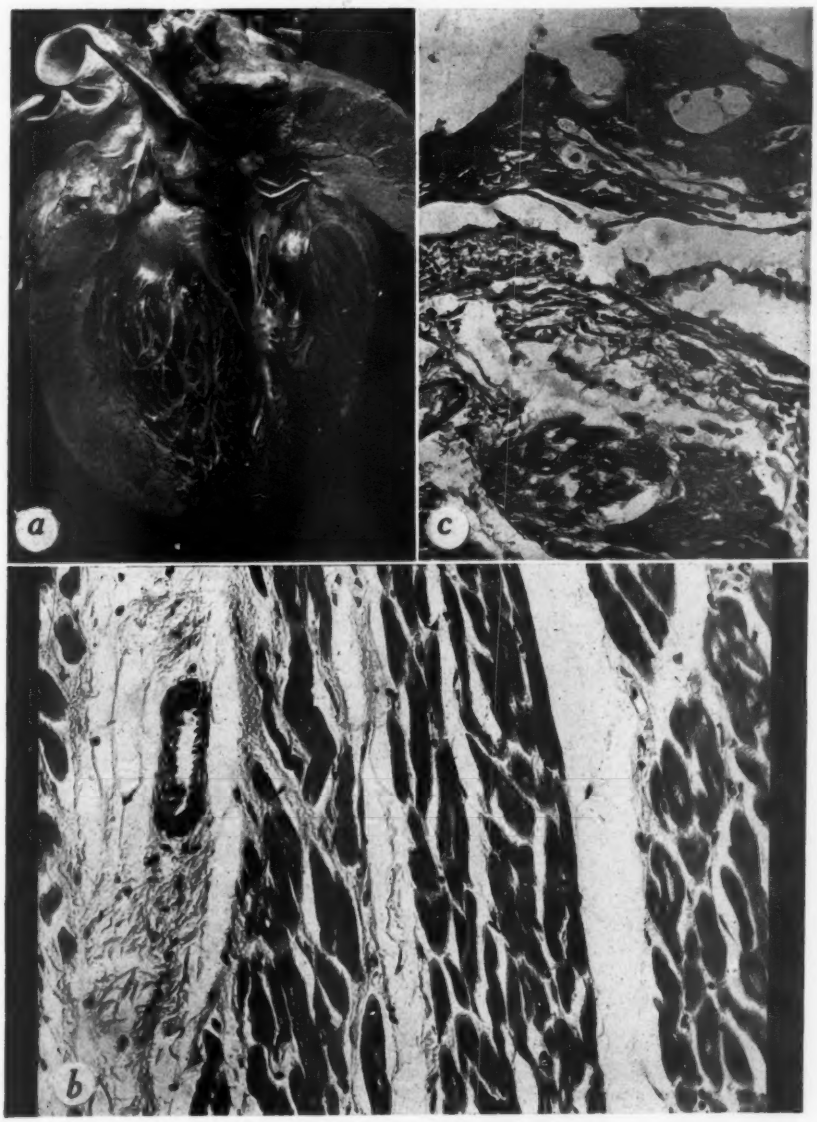

Fig. 2.—Patient 1. Heart. *a*, Severe hypertrophy and moderate dilatation of left ventricle. *b*, Normal myocardium (hematoxylin and eosin ×175). *c*, Fibrinous exudate on epicardium of left auricle (hematoxylin and eosin ×150).

Histologic Examination.—Sections of the myocardium appeared normal (Fig. 2*b*). Sections of the epicardium revealed a fibrinous exudate containing very few cellular elements. There was beginning organization of this exudate by fibroblasts from the epicardial surface.

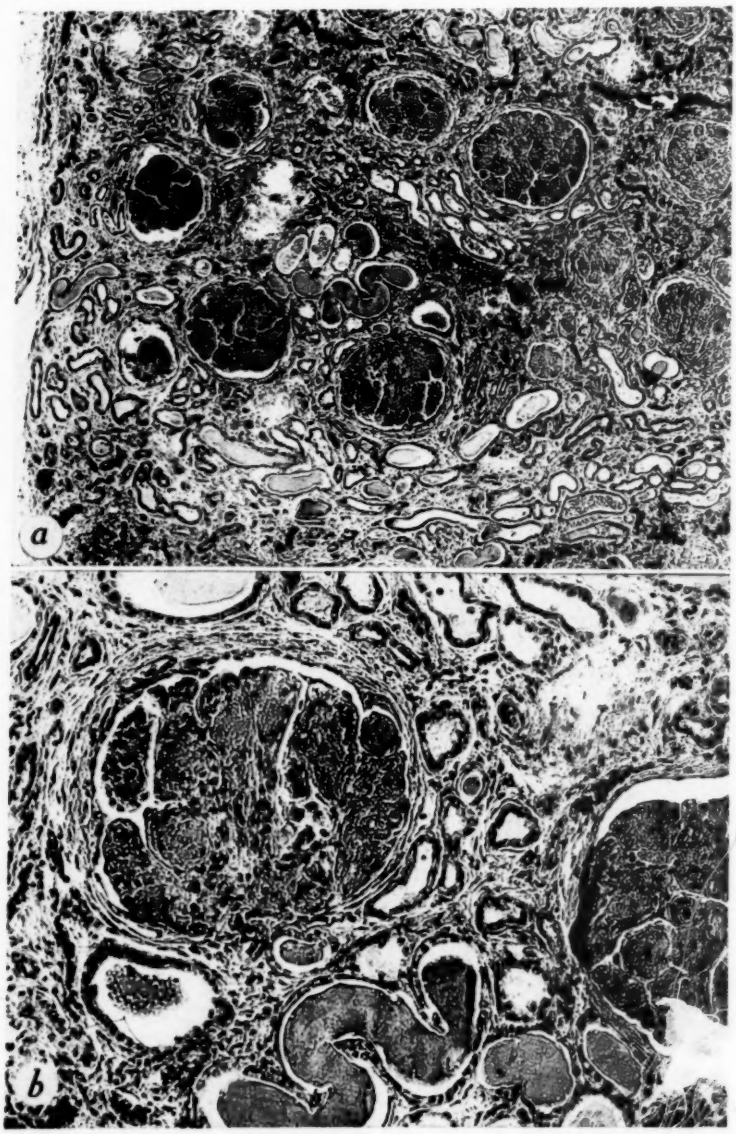

Fig. 3.—Patient 1. Kidney. *a*, Hyalinization of glomeruli; dilatation of some tubules and atrophy of others; casts and erythrocytes in tubules; increase of interstitial connective tissue and lymphocytes (hematoxylin and eosin ×50). *b*, Same (hematoxylin and eosin ×150).

The appearance was consistent with that of so-called uremic pericarditis (Fig. 2*c*).

Sections of the right lung revealed progressive, nodular, caseous tuberculosis in the upper lobe. Sections from the lower [illegible] of the same

lung revealed tuberculous bronchopneumonia with much caseation. Between the regions of caseation, the alveoli were filled by large, clear, vacuolated phagocytic cells and lymphocytes. The ulcers in the ileum proved to be tuberculous in histologic sections.

Sections of both adrenal glands appeared normal.

Examination of many sections of both kidneys failed to reveal a single normal glomerulus. Most of the glomeruli were increased in size, and the capillaries were largely obliterated by an acidophilic, homogeneous, hyaline material (Fig. 3, *a* and *b*). The endothelial cells were encased by the homogeneous material and usually were diminished in numbers. Occasionally, glomeruli were observed in which some of the capillaries were still patent. Synechiae and epithelial crescents were numerous. The tubules were generally collapsed and lined by atrophied epithelium. A few of them were dilated, and most of them contained precipitated albuminous material. Lymphocytes and interstitial connective tissue were increased in amount. The arteries and arterioles revealed sclerosis graded 2.

The following anatomic diagnoses were made: (1) chronic glomerulonephritis, (2) fibrinous pericarditis, (3) hypertrophy of heart (hypertension), (4) chronic tuberculosis of the lungs, with tuberculous pneumonia and chronic tuberculosis of hilar nodes, (5) tuberculous ulcer of ileum, and (6) pseudomembranous esophagitis.

The duration of the renal disease in this case was three years and seven months.

CASE 2.—The patient, aged 61 years, was an accountant. There were no facts in the family history pertinent to his present illness. As a child he had suffered from asthma. He had had pneumonia at the age of 23 years, pleurisy at 31, and influenza in 1918, when he was 39 years old. He also had had tonsillitis before 1920. Since May, 1939, or a year before the onset of the present illness, the patient had felt a heavy sensation under the lower part of the sternum, usually after the first swallow of solid food at the evening meal. This sensation was relieved by drinking water; however, four or five times a week he would vomit most of his supper within an hour after ingestion of the meal. The onset of cardiac symptoms occurred in May, 1940, seven months before admission, when dyspnea developed rather suddenly on exertion. Ten days later orthopnea became severe and edema developed. The patient was confined to bed for two months, and at the end of this period seemed to be greatly benefited by this rest. He was up and about from July 18 to October 1. On this latter date orthopnea and edema forced him to bed again. For the eight weeks preceding admission, coughing and nocturnal dyspnea had been the most irritating symptoms. The patient had noticed a diminishing volume of urine for some time. Treatment had consisted of digitalis and sedatives and three injections of merbaphen during November.

The patient was admitted to the hospital Nov. 27, 1940. He weighed 136 pounds (61.8 kg.), and his height was 65 inches (165 cm.). He was orthopneic, and considerable dependent edema was present, including the scrotum. The heart was enlarged, tachycardia was present, and some of the heartbeats did not produce a pulse in the radial artery. The heart sounds were distant. Gallop rhythm could be heard, but no murmurs. There were numerous moist râles throughout the lungs and signs of fluid in the right lower portion of the thorax. There was also

evidence of congestion of the liver; the edge was easily palpated 5 cm. below the costal margin. The blood pressure was 115/85. Dr. Wagener reported that the ocular fundi were essentially normal. Routine urinalyses, four in all, showed a specific gravity of 1.014 to 1.024, albumin, grade 1 to 2, no reducing substances, and a sediment containing hyaline casts, grade 3, and leucocytes, grade 1. There was no anemia; the erythrocytes numbered 4,480,000 per c.mm. The blood flocculation reaction for syphilis was negative. A roentgenogram of the thorax revealed an enlarged heart shadow (greatest diameter, 17 cm.) and some congestion at the bases of both lungs. The clinical picture was that of chronic myocardial degeneration and failure, with severe chronic passive congestion of the lungs, liver, and kidneys.

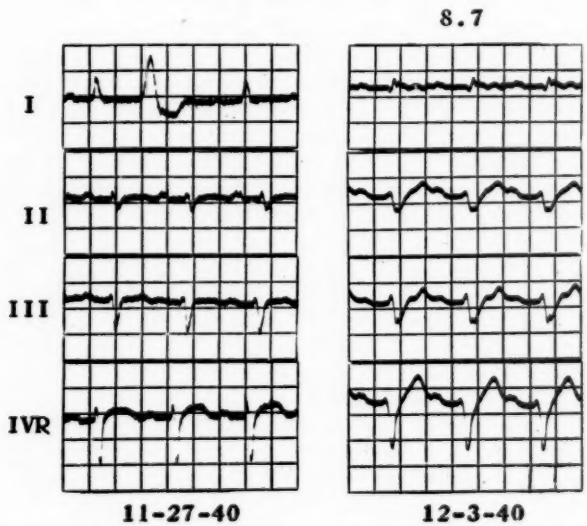

Fig. 4.—Electrocardiograms of Patient 2. The first tracings (11/27/40) show low amplitude, with slurring of the QRS complexes, isoelectric T waves in the standard leads, and left axis deviation. There are delayed auriculoventricular conduction (P-R = 0.24 second) and a few premature beats of ventricular origin. The second tracings (12/3/40) show that a marked intraventricular conduction defect (QRS = 0.16 second) has developed, with the P-R interval remaining the same; note potassium content of serum in milliequivalents.

Course in the Hospital from November 27 to December 7.—The blood pressure was measured each morning. It varied from 100 to 130, systolic, and 80 to 100, diastolic. The volume of urine voided in twenty-four hours was decidedly reduced, varying from 100 to 125 c.c. The clinical picture was characterized by vomiting, oliguria, increasing edema, and the rapid development of uremia. The blood urea increased from 48 mg. on November 27 to 246 mg. on December 6. On December 2 the patient began to be drowsy, and, on December 5, confused and stuporous, and from then until death, on December 7, there was increasing cardiac and renal failure. The administration of 12 Gm. of potassium nitrate in forty-eight hours during November 29 to December 1, of 2 c.c. of salyrgan on November 28, and of 2 c.c. of mercupurin on December 1 did not produce any diuresis, and therefore the use of these drugs was discontinued. Two electrocardiograms were taken, the first on November 27 and the second on December 3. The latter revealed a distinct intraventricular conduction defect (Fig. 4). On

December 3 there was also a high serum potassium concentration of 8.7 milliequivalents in 1,000 c.c. These findings were similar to those in Case 1. On December 6 a second estimation of the serum potassium revealed a concentration of 8.8 milliequivalents in 1,000 c.c. (Table II).

Necropsy.—There was severe edema of the legs and scrotum. The peritoneal cavity contained 200 c.c. of clear yellow fluid. There were 700 c.c. of clear, straw-colored fluid in the right pleural cavity, and 350 c.c. in the left pleural cavity.

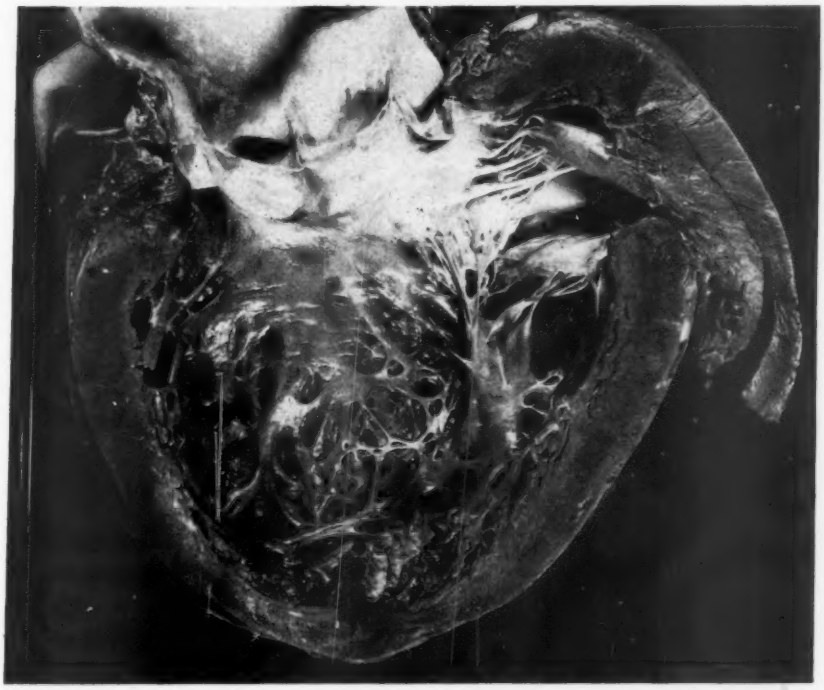

Fig. 5.—Patient 2. Heart. Hypertrophy and severe dilatation of left ventricle with mural thrombi.

The heart weighed 485 grams. In the right auricle, at the orifice of the coronary sinus and immediately above the tricuspid valve, there was an old organized thrombus which measured 1.5 cm. in its widest extent. There were mural thrombi at the base of the right ventricle and also on the left lateral wall and apex of the left ventricle. The left ventricle was greatly dilated (Fig. 5). There was mild sclerosis of the coronary arteries.

There were mild congestion and edema of the lungs. Many of the small arteries of the lower lobes contained emboli and thrombi. There were recent, small infarcts in the regions supplied by these vessels.

The liver weighed 1,022 grams. The surface was smooth, but the markings were greatly increased on the cut surface. The so-called nutmeg appearance was present.

On the posterior wall and greater curvature of the stomach there were two superficial ulcers which had raised borders. The larger measured 4 by 1 cm., and the smaller, 2 by 1 cm. The jejunum and the

TABLE II

DATA ON BLOOD OF PATIENT 2

DATE	HOSPITAL DAY	WHOLE BLOOD			BLOOD SERUM					BLOOD PLASMA		ECG
		HGB., GM. IN 100 C.C.	UREA, MG. IN 100 C.C.	CREATININE, MG. IN 100 C.C.	PROTEIN, GM. IN 100 C.C.	ALBUMIN, GM. IN 100 C.C.	POTASSIUM		SULFATE, MG. IN 100 C.C.	CHLORIDE, MG. IN 100 C.C.	CO_2 COMBINING POWER, VOL. IN 100 C.C.	
							MG. IN 100 C.C.	MEQ. IN 1,000 C.C.				
11/27/40	1	15.5	48									ECG
11/28/40	2				6.9	3.3						
11/29/40	3		74	2.2								
12/ 2/40	6		120	4.2					18			
12/ 3/40	7		142	4.8			34.2	8.7		500	46	ECG
12/ 4/40	8		162	5.1								
12/ 5/40	9		196	6.4								
12/ 6/40	10		246	6.8			34.4	8.8				
12/ 7/40* 11:22 P.M.	11											

*Patient died.

ileum were moderately congested. There were numerous small hemorrhages in the colon, measuring from 0.5 to 1.5 cm. in diameter. Some of these hemorrhagic regions were covered by a pseudomembranous exudate.

The right kidney weighed 182 grams. The surface was finely granular. There were one small cortical adenoma and two small scars which measured approximately 0.7 cm. in diameter. The left kidney weighed 165 grams and was not remarkable, grossly.

Fig. 6.—Patient 2. Scar of the interventricular septum of the heart (hematoxylin and eosin ×150).

Histologic examination.—In sections of the mural thrombus in the right auricle there were organization by fibroblasts and slight atrophy of the muscle fibers beneath the thrombus. In the thrombi of the right and left ventricles, also, organization had occurred, and there was also focal atrophy of the muscle fibers. Sections of the interventricular septum revealed moderate fatty metamorphosis in the muscle fibers and occasional foci of scarring (Fig. 6). In sections of the liver there was severe chronic passive congestion, with atrophy and necrosis of the cells in the central portions of the lobules.

Sections of the stomach revealed recent ulcerations of the mucosa. There were dilated capillaries and venules, together with small hemorrhages and thromboses in the base of the ulcers.

There were foci of atrophy, occasional collections of lymphocytes, and chronic passive congestion in sections of the adrenal glands.

In sections of the kidneys there was evidence of moderate, chronic, passive congestion. There were also foci of tubular atrophy, sometimes associated with hyalinized glomeruli (Fig. 7, *a* and *b*). Arteriolar sclerosis was mild. There was an old pyelonephritic scar in the right kidney.

The following anatomic diagnoses were made: (1) hypertrophy of heart (485 grams); (2) dilatation of left ventricle, with cardiac de-

compensation; (3) hydrothorax (right, 700 c.c., left, 350 c.c.), ascites (200 c.c.), and subcutaneous edema of legs; (4) mural thrombi of right auricle and both ventricles; (5) organizing infarct of right lung, with chronic pleuritis; (6) chronic passive congestion of stomach, with recent ulcers; (7) chronic passive congestion and atrophy of liver; (8) multiple hemorrhages of cecum; and (9) mild fatty metamorphosis of the myocardium.

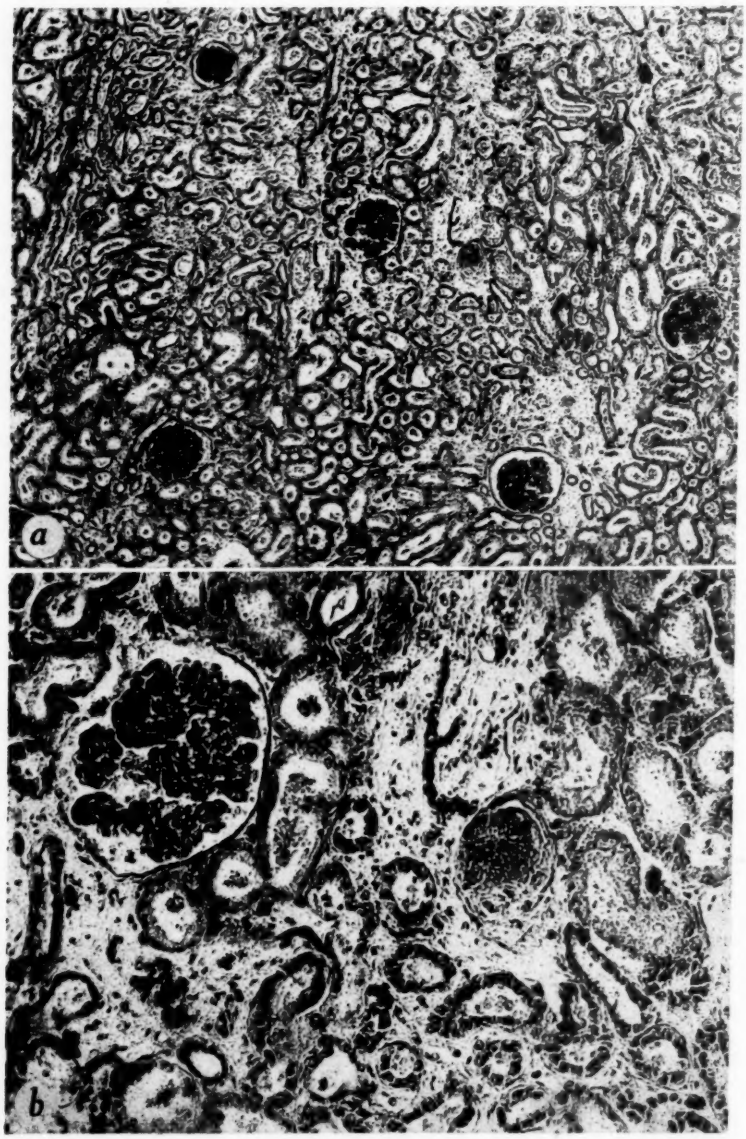

Fig. 7.—Patient 2. Kidney. *a*, Chronic passive congestion; foci of tubular atrophy (hematoxylin and eosin ×50). *b*, Same (hematoxylin and eosin ×150).

The duration of the chronic myocardial disease in this case was seven months, and that of the acute or subacute renal insufficiency, a few weeks.

CASE 3.—The patient was a married woman, aged 35 years, who first visited the Mayo Clinic Aug. 4, 1942. Her family history failed to reveal any facts of importance with regard to her present illness. The patient married at the age of 19 years, and had two healthy children, aged 14 and 12 years. There was no record of any serious illness in childhood or of untoward symptoms during her pregnancies. Her chief complaint was of irregular vaginal bleeding which had begun in February, 1942, six months before admission. On physical examination the patient appeared in good condition except for moderate anemia. She weighed 112½ pounds (51.0 kg.) and was 63 inches (160 cm.) in height. The heart seemed normal, and the blood pressure was 120/80. On vaginal examination one could see and feel an infiltrating type of carcinoma involving the cervix of the uterus. Further study revealed secondary anemia; the hemoglobin was 9.3 Gm. in 100 c.c., and the erythrocyte count, 3,500,000 per cubic millimeter. The blood flocculation reaction for syphilis was negative. The results of routine urinalysis were normal, as was the blood urea (24 mg. in 100 c.c.).

On August 17, Dr. Counseller performed abdominal hysterectomy according to the Wertheim technique, and, from the tissues removed, the pathologist made a diagnosis of carcinoma of the cervix and metastatic involvement of the tissues near the lower portion of the left ureter. The patient's postoperative course was very satisfactory. Subsequently, radium and roentgen therapy were used, and the patient left for home on September 16.

Interim History.—The patient felt well until the end of November. At that time nausea and vomiting, oliguria, and general edema developed. Actual anuria for six days occurred late in December. Ascites became marked at this time. Fluid was administered by vein, and soon the volume of urine increased and the edema and other symptoms subsided. The patient remained fairly well for the next two months. Her reasons for returning to the clinic were persistent thirst, polyuria, general weakness, and edema of the ankles.

Second Admission to the Mayo Clinic, March 17, 1943.—The patient weighed 101 pounds (45.9 kg.). She looked pale. There was no demonstrable edema. On bimanual palpation of the pelvis nothing abnormal was felt. The blood pressure was 120/80. A roentgenogram of the thorax was reported as not showing any abnormality except some calcified deposits in the lymph nodes of the hila of the lungs. The patient was observed in the hospital for a period of seventeen days—from March 19 to April 4. Routine urinalysis revealed a specific gravity of 1.003 to 1.011, no reducing substances, but albumin grade 1 to 2, and an occasional leucocyte in the sediment. The blood urea was increased to 172 mg., and the creatinine, to 6.0 mg. During the patient's stay in the hospital the blood urea fell to 140 mg. (Table III); the volume of urine in twenty-four hours increased from 1,600 to 3,000 c.c., and she felt distinctly better. Intravenous therapy included 5 and 10 per cent solutions of glucose and two transfusions of 250 c.c. of citrated whole blood. The patient was up and about in town for the next nine days. She re-entered the hospital on April 13 because of nausea and vomiting.

Table III

Data on Blood of Patient 3

Date	Whole blood			Blood serum								Blood plasma				ECG
						Potassium										
	Hgb., gm. in 100 c.c.	Urea, mg. in 100 c.c.	Creatinine, mg. in 100 c.c.	Protein, gm. in 100 c.c.	Albumin, gm. in 100 c.c.	mg. in 100 c.c.	meq. in 1,000 c.c.	Sodium, mg. in 100 c.c.	Calcium, mg. in 100 c.c.	Phosphorus, mg. in 100 c.c.	Sulfate, mg. in 100 c.c.	Chloride, mg. in 100 c.c.	Cholesterol, mg. in 100 c.c.	pH	CO_2 combining power vol. %	
8/15/42	9.3	24														
3/18/43	6.3	172	6.0													
3/19/43												603			36	
3/23/43		100	4.4													
3/25/43	9.3															
3/27/43		130	5.6													
4/ 1/43		140	6.4									538			37	
4/13/43		218	10.8									602			35	
4/14/43		206									21				43	
4/19/43		200	13.6									462			40	
4/20/43		204	15.2			26.4	6.8					495				
4/21/43						27.4	7.0	293		8.8	23					ECG
4/23/43		201	16.8			26.8	6.9					528				ECG
4/26/43		183	15.2			24.6	6.3					544			42	ECG
4/30/43		132	11.2			20.4	5.2					507				ECG
5/ 7/43		160	8.8			26.3	6.7				15	596			39	ECG
5/10/43	8.0	177	9.6												45	
5/12/43		165				30.5	7.8				16	561			50	ECG
5/15/43		132	10.8			23.1	5.9									ECG
5/19/43	8.5	150	14.4	7.0*	4.4	23.9	6.1		9.7	6.6	15	540			50	ECG
5/22/43		165	16.8			26.2	6.7									ECG
5/31/43		246	18.0			32.1	8.2		9.7	4.8	27	468			31	ECG
6/ 3/43	7.8	267	22.0			36.6	9.4		9.1	10.1						ECG
6/ 4/43 10:00 A.M.														7.35†	32†	
10:55 A.M.						36.8	9.4	262	9.5							ECG‡
2:55 P.M.		291	21.0	6.1*	3.7					12.5	16	511	175§		25	
11:55 P.M. Pt. died																

*Nonprotein nitrogen of serum 120 and 192 mg. per cent, respectively.
†Oxalated blood withdrawn from arm vein under oil. CO_2 determined directly. pH determined (glass electrode) by Dr. Power.
‡Electrocardiogram taken and blood serum withdrawn for estimation of potassium concentration thirteen hours before death.
§Concentration of cholesterol esters 104, lecithin 169, fatty acids 366, and total lipoids 541 mg. per cent, respectively.

Course in Hospital April 13 to June 4, Fifty-Three Days.—On admission there was no demonstrable edema. The patient's weight was 100 pounds (45.4 kg.). Tachycardia was present, and gallop rhythm was heard over the cardiac apex. Her breath had a uremic odor and the blood urea had increased to 218 mg. Ophthalmoscopic examination revealed anemic fundi, with two small hemorrhages in the left retina which were considered to be secondary to the general anemia. The specific gravity of the urine varied from 1.002 to 1.010. The concentration of protein in the urine was accurately estimated in three twenty-four-hour collections of urine and found to be 0.09 to 0.8 per cent. A rare hyaline cast and a few to a moderate number of leucocytes were observed in the urinary sediment.

The volume of urine for the twenty-four-hour period, April 14 to 15, was 3,050 c.c. It gradually decreased to only 200 c.c. on April 18 and 19, but increased to 1,600 c.c. on April 23. On April 20 cystoscopic examination was done. The bladder and ureteral orifices appeared to be normal, but the ureteral catheter met definite resistance in both ureters at approximately 4 cm. from their vesical orifices. Passage of the catheters beyond the obstructions was not attempted. On April 21 the first of a series of twelve electrocardiograms was taken, and the concentration of serum potassium was found to be increased to 7.0 milliequivalents in 1,000 c.c.

TABLE IV

DISTRIBUTION OF ELECTROLYTES IN BLOOD PLASMA AND SERUM OF PATIENT 3*

BASE			ACID		
	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.		MG. IN 100 C.C.	MEQ. IN 1,000 C.C.
Sodium	262.0	114.0	Chlorides	306.0	86.3
Potassium	36.8	9.4	Bicarbonate	32.0†	13.5
Calcium	9.5	4.7	Phosphates	12.5	7.3
			Sulfates	16.0	3.3
			Protein	6.1‡	14.8
Total meq.		128.1§			125.2

*Blood withdrawn 6/4/43 at 10:00 A.M., 10:55 A.M., and 2:55 P.M.

Estimations made in oxalated blood plasma—chlorides, bicarbonate.

Estimations made in blood serum—sodium, potassium, calcium, phosphates, sulfates, proteins.

†Blood withdrawn (oxalated) under oil, carbon dioxide content, volumes in 100 c.c. Plasma pH 7.35 estimated by glass electrode by Dr. Power.

‡Protein concentration estimated Gm. in 100 c.c. serum. Base meq. per liter bound by protein = 0.243 times Gm. protein per liter.[25]

§Magnesium was not estimated. Usual concentration among similar patients with uremia 2 to 3 meq.

With the rise in the volume of urine to 1,600 c.c. on April 23, diuresis began, and, on the following days, the volume rose to 1,775 and 2,750 c.c. This diuresis was accompanied by loss of weight, diminishing edema, improvement of the patient's well-being, and a fall of the concentration of urea, creatinine, and potassium in the blood; the potassium decreased to a normal concentration of 5.2 milliequivalents in 1,000 c.c. (Table III). The high fluid intake during this period included intravenous injections of solutions of 5, 10, and 20 per cent glucose, 5 per cent sodium bicarbonate, 0.9 per cent sodium chloride, and 50 per cent sorbitol. Theophylline with ethylenediamine was often added to these solutions in amounts of 0.25 to 0.5 Gm.

On May 1, thrombophlebitis developed in the left femoral vein. From May 15 to June 4, when the patient died, she grew progressively worse. There were a gradual increase of edema and a corresponding gain of

weight to 117 pounds (53.1 kg.). Nausea and vomiting became very troublesome. Renal insufficiency steadily increased as oliguria developed. On May 12, mild pulmonary edema occurred and gallop rhythm was present. On May 18 the blood pressure was 210/120. On May 18 and May 20 convulsive seizures developed. The blood pressure on May 20 was found to be 220/115. The concentration of potassium in the blood serum on May 31 had increased to 8.2 milliequivalents in 1,000 c.c., and continued to increase to 9.4 milliequivalents on June 3 and June 4 (Table III). On these two latter days the electrocardiograms revealed partial auriculoventricular block and intraventricular block (Fig. 8). Changes in the concentration of other electrolytes in the blood at this time are also of interest (Table IV). During the morning of June 4 the patient was drowsy and complained of a great deal of nausea. The blood urea and creatinine had risen to 291 and 21 mg. per 100 c.c., respectively. At 11:55 P.M. the patient died.

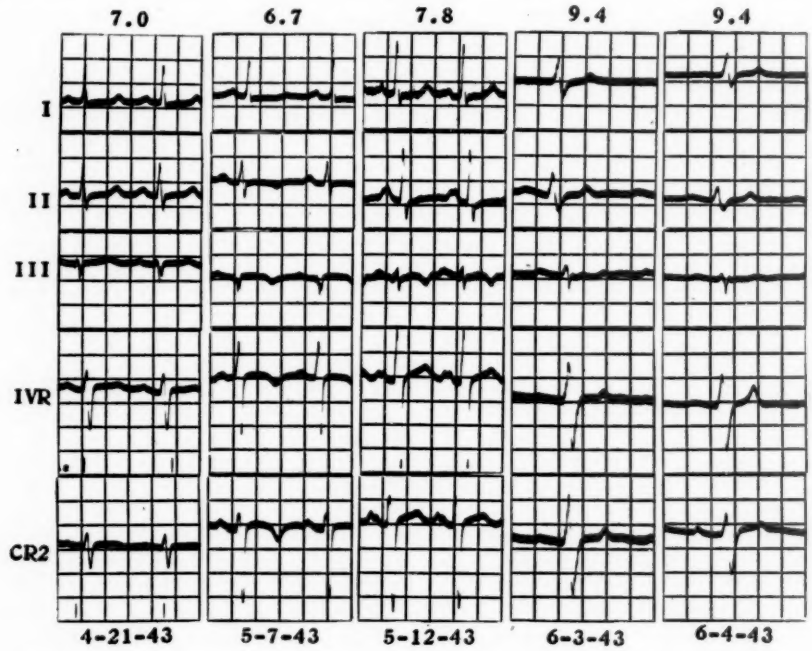

Fig. 8.—Electrocardiograms of Patient 3. The first tracings (4/21/43) show only left axis deviation and a slightly prolonged electric systole (QT = 0.32; QT/$\sqrt{\text{cycle}}$ = 0.41). The next tracings (5/7/43) show diphasic T waves in Lead I and negative T waves in all other leads. This picture, as described in the text, is sometimes associated with left ventricular hypertrophy. In the following tracings (5/12/43) the T waves in Lead I and chest leads have returned to an upright position. The next tracings shown (6/3/43) illustrate a lowering of the amplitude of the P waves, an increase of auriculoventricular conduction (P-R = 0.24 second), and the development of an intraventricular conduction defect (QRS = 0.16 second). The tracings taken the following day are very similar, and also to be noted is the sharp "peaked" T wave, with the narrow base in the apical chest lead. Note potassium content of serum in milliequivalents.

The clinical diagnosis in this case was bilateral, chronic hydronephrosis and pyelonephritis, secondary to bilateral ureteral obstruction due to metastatic carcinoma, renal insufficiency, uremia, hypertension, myocardial failure, and left ileofemoral thrombophlebitis.

Necropsy.—There was moderate subcutaneous edema which extended cephalad as far as the breasts. The left leg and thigh were noticeably

larger than the right. The peritoneal cavity contained approximately 1,500 c.c., and each of the pleural cavities contained approximately 1,000 c.c., of clear yellow fluid. In the left pleural cavity there were old fibrous adhesions situated laterally, anteriorly, and on the diaphragmatic surface. The transverse diameter of the pericardium was 15 cm., and the pericardial sac contained approximately 150 c.c. of clear yellow fluid.

The heart weighed 465 grams, as compared with an estimated normal of 250 grams, but was not otherwise remarkable. Coronary sclerosis was mild, grade 1.

There was a recent infarct 2 cm. in diameter in the upper lobe of the right lung. The lungs were not remarkable otherwise.

The gall bladder contained approximately 15 c.c. of dark brown bile. The mucous membrane appeared normal. There were four angular, shiny, black stones, approximately 3 mm. in diameter, in the cystic duct, and one in the gall bladder.

The stomach contained approximately 50 c.c. of clotted blood. There were moderate edema and congestion of the mucous membrane.

An irregular, firm mass, which measured 2.5 by 1.5 by 1 cm., surrounded and constricted the right ureter at a point 3 cm. cephalad to the ureteral orifice of the bladder. There was a similar mass 3 cm. in diameter around the left ureter at a point 2 cm. cephalad to the ureteral orifice. The ureters above the obstructing lesions and the pelves and calices of both kidneys were moderately dilated (Fig. 9). Aside from the hydronephrosis, the kidneys were not grossly remarkable. The right kidney weighed 174 grams, and the left kidney, 140 grams.

The upper portion of the left femoral vein was compressed by a small mass of firm white tissue. A firm gray thrombus occluded the left femoral and iliac veins in this region.

Histologic Examination.—Sections of the interventricular septum of the heart were normal for the most part. Rarely, small focal regions of atrophy and fibrosis could be observed (Fig. 10).

Sections from the region of increased consistency in the upper lobe of the right lung revealed an infarct which was undergoing organization at the edges. There were deposits of calcium in the alveolar septa and in the smaller vessels at the edge of the infarct. In sections of the liver there was moderate chronic passive congestion, with atrophy of the cells in the region of the central veins. There was mild chronic passive congestion in the adrenal glands.

In sections of the right ureter there were nests of squamous carcinoma cells throughout the wall, as well as in the connective tissue surrounding this structure. The neoplasm had grown into the submucosa and mucosa of the ureter, and, although a lumen was still present, it was definitely compromised (Fig. 11). The sections of the left ureter revealed a similar appearance.

In the sections of the right kidney there were moderate dilatation and atrophy of all tubules, together with an increase of interstitial connective tissue. Focal collections of lymphocytes and occasional accumulations of polymorphonuclear cells were observed (Fig. 12, *a* and *b*). There was dilatation of Bowman's capsule, but the glomerular tufts appeared normal. The left kidney was similar in appearance. There was mild arteriolosclerosis in both kidneys.

Sections of the left femoral vein revealed invasion of the wall by squamous-cell carcinoma. A partially organized and canalized thrombus occluded the lumen.

Fig. 9.—Patient 3. Obstruction of ureters by carcinoma with ureterectasis, hydronephrosis, and mild chronic pyelonephritis.

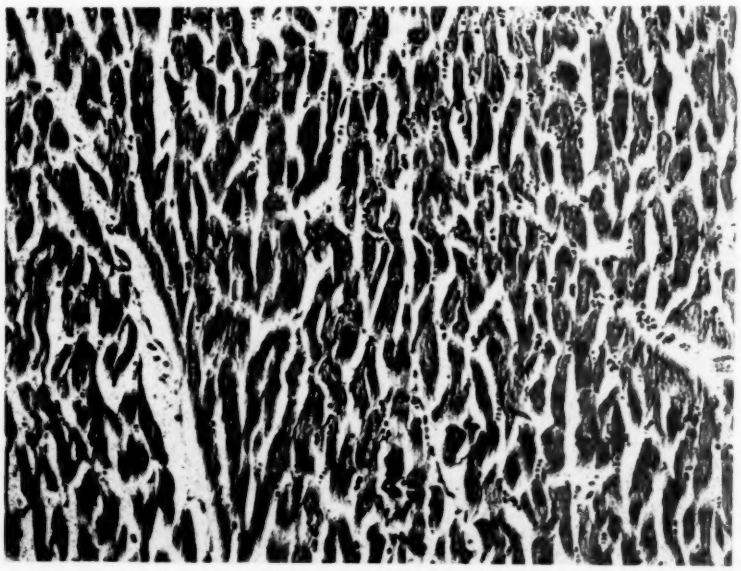

Fig. 10.—Patient 3. Interventricular septum; normal myocardium (hematoxylin and eosin ×150).

The following anatomic diagnoses were made: (1) ancient (Aug. 17, 1942) abdominal Wertheim hysterectomy for squamous-cell carcinoma of the cervix; (2) recurrent carcinoma, with obstruction of both ureters; (3) bilateral hydronephrosis and chronic pyelonephritis, with atrophy of kidneys; (4) metastatic carcinoma of left femoral vein, with organized thrombus; (5) organizing infarct of right lung; (6) bilateral hydrothorax (1,000 c.c. each), ascites (1,500 c.c.), and subcutaneous edema; (7) hypertrophy of heart (465 grams) (hypertension); and (8) gastric hemorrhage (50 c.c.).

Summary of Renal Insufficiency.—Symptoms of renal dysfunction began approximately ten months after cancer of the cervix was suspected and three and a half months after hysterectomy. Four periods of severe renal insufficiency developed between December, 1942, and June, 1943. Temporary improvement of renal function occurred after three of these periods. Death occurred when the patient had uremia, six months after the onset of symptoms due to renal insufficiency.

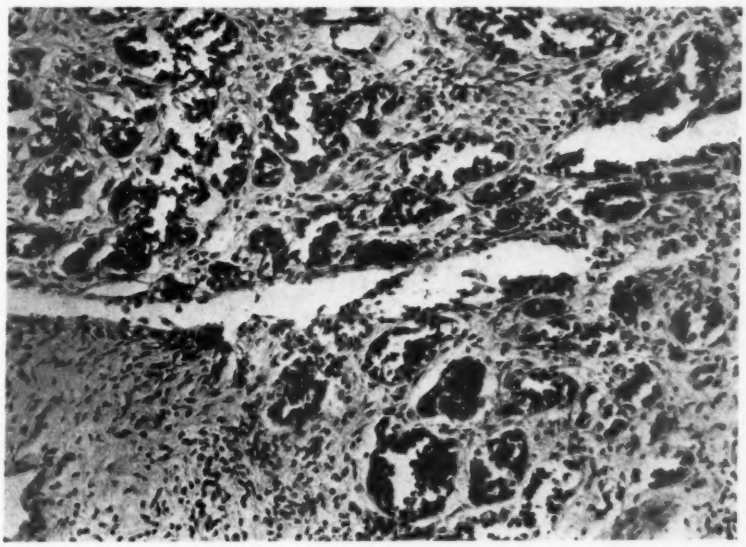

Fig. 11.—Patient 3. Squamous-cell carcinoma in wall of the right ureter (hematoxylin and eosin ×150).

OBSERVATIONS

Clinical and Pathologic Observations.—Severe uremia and oliguria were present in each of the cases when potassium intoxication was suspected. In Cases 1 and 3 the renal insufficiency and uremia were chronic, whereas, in Case 2, severe renal impairment and uremia were acute and present for only a week. Hypertension was noted in two of the cases, but was absent in Case 2 during the period of observation. The concentration of hemoglobin in the blood varied considerably in these cases—from normal to that of severe anemia. The cause and type of renal pathologic change were distinctly different in each case. The primary renal lesions were chronic glomerulonephritis in Case 1, chronic hydronephrosis and pyelonephritis secondary to ureteral obstruction

in Case 3, and chronic passive congestion secondary to myocardial failure in Case 2.

Our experience in Case 2 seemed unusual. However, Scholtz,[7] in 1932, reported an increased concentration of potassium in the serum of three patients, and commented on the absence of a renal pathologic process other than passive congestion. Bywaters[8] recently observed similar changes in the blood and electrocardiograms of patients suffering from acute renal insufficiency and uremia due to crush injuries of

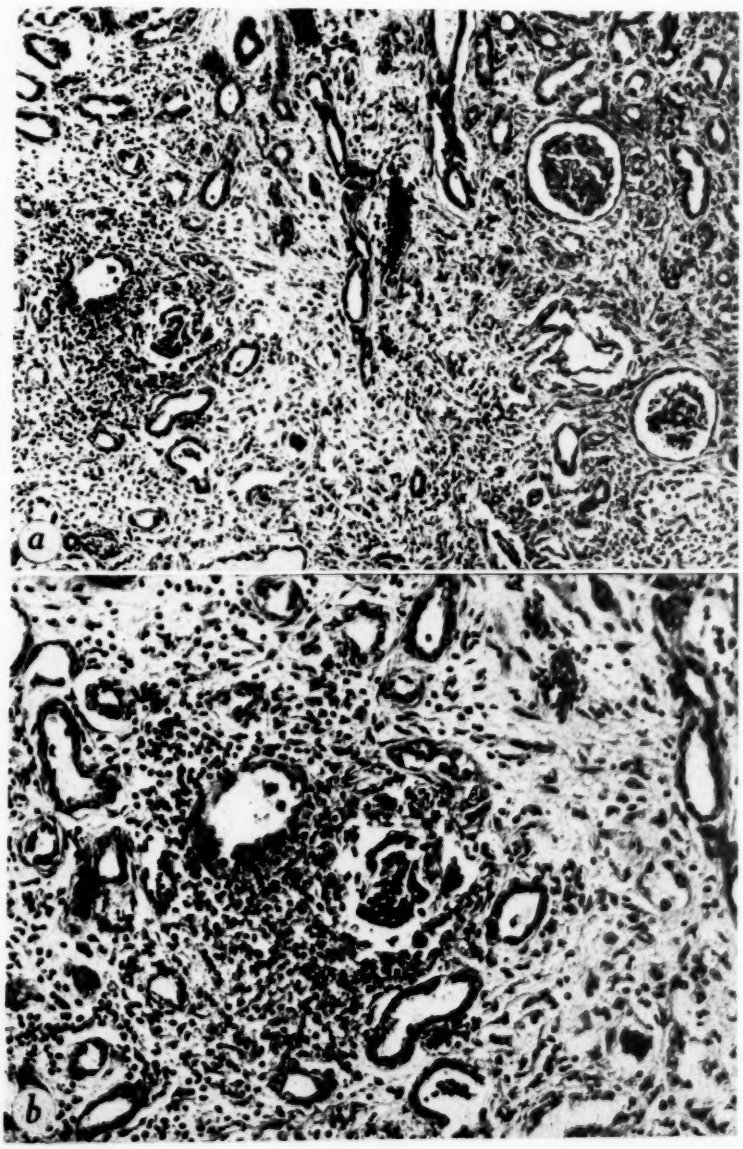

Fig. 12.—Patient 3. Kidney. *a*, Atrophy of tubules, foci of leucocytes and increased interstitial connective tissue (hematoxylin and eosin ×110). *b*, Same (hematoxylin and eosin ×180).

the extremities. Therefore, it seems evident that the combination of uremia, increased serum potassium, and characteristically abnormal electrocardiograms occurs among patients suffering from both acute and chronic uremia. Hypertrophy of the heart and myocardial failure were present in all three cases before the marked increase of serum potassium and electrocardiographic alterations occurred. However, significant histopathologic lesions in the myocardium were found only in Case 2 (Fig. 6). The absence of distinct disease of the coronary arteries in these cases is worthy of comment. The presence of pericarditis in Case 1 and its absence in Cases 2 and 3 are also of interest.

Chemical Studies of the Blood.—Serious renal dysfunction was evident in the three cases at the period when the concentration of potassium in the blood serum was very high (8.7 to 10.5 milliequivalents in 1,000 c.c.), and changes had occurred in the electrocardiogram. These increased concentrations of potassium in the serum of our patients closely approximate the highest values reported in the serum of uremic patients.* The highest concentration noted in the literature was 11.6 milliequivalents.[9] Evidence of renal insufficiency was best indicated by marked retention of urea and creatinine in the blood stream; the concentration of urea increased to 246 to 392 mg. and that of creatinine to 6.8 to 22 mg. in 100 c.c. of blood. This degree of uremia presented an important, but complex, chemical problem. Special consideration was given to changes that occurred in the concentration of individual electrolytes and the acid-base equilibrium in plasma or serum. Associated with the marked and sustained increase in the concentration of potassium in the serum of these patients were an increase of sulfates and a slight to moderate decrease of the carbon dioxide combining power. The latter was indicative of acidosis, a common feature of uremia.

The concentrations of several lipoid constituents and a majority of the electrolytes were ascertained in Case 3 during the last day of the patient's illness, June 4. The concentration of the lipoid constituents was normal. The concentrations of potassium, sulfate, and phosphate were greatly increased; those of sodium, chloride and bicarbonate, were distinctly decreased. The concentrations of calcium and protein were normal. It is of interest that, with these definite quantitative alterations of both basic and acid components, the hydrogen ion concentration, or pH, of the plasma was within the normal range.[25] This nicety of balance between acid and basic radicles is also revealed by the relatively close approximation of the total milliequivalents of each. These values, 125 to 130 milliequivalents, are considerably lower than those observed among normal persons and in many cases of nephritis (Table IV). In 1928, Salvesen[10] reported similar low values for total base and total acid in a case of chronic glomerulonephritis during the terminal stage of uremia. In computing the total base in the serum of Patient 3, the

*We are referring to estimations of the concentration of potassium in the blood serum of uremic patients made since the introduction of a satisfactory micromethod.

amount of potassium relative to that of sodium is small. This indicates that the toxic action of the increased amount of potassium in the serum and tissue cells is not simply due to an increase of base per se.

The fluctuations of the concentration of potassium in the blood serum of Patient 3, during her stay of six weeks in the hospital, are interesting. The decrease from 6.8 milliequivalents on April 20 to 5.2 milliequivalents, a normal concentration, on April 30, was associated with improvement of renal function. Similar observations were made in a single case among a previous series of cases in which there was uremia.[1, 11] Later, in Case 3, the concentration of potassium increased to 7.8 milliequivalents (May 12). This increase was apparently temporary, for the concentration fell in three days to 5.9 milliequivalents. In contrast to these earlier fluctuations of the serum potassium there was a progressive rise from 6.7 to 9.4 milliequivalents during the terminal phase, from May 22 to June 4 (Fig. 13).

Electrocardiographic Observations.—It has been noted by us and others[6, 12-15] that increased serum levels of potassium are associated with rather characteristic electrocardiographic changes. Among normal persons, induced, mild hyperpotassemia causes increased height of the T waves, and the degree of increase of serum potassium correlates well with the increase in height of the T wave. Frequently this change becomes quite distinctive, in that the base of the T wave becomes narrower than normal and the apex sharp or "peaked." With greater and more sustained increases of serum potassium, as we have observed in our three cases of severe renal insufficiency, partial auriculoventricular block and intraventricular block may develop. The exact locus of the intraventricular block is unknown to us, and we feel that it would be wrong and misleading categorically to place it in the main bundle branches.

In regard to Case 1 it will be noted that pericarditis developed, and it is well known that this condition can alter the electrocardiogram greatly.[16, 17] In this connection it is of interest that we have observed in a case of uremia and pericarditis an electrocardiogram that was typical of pericarditis when the concentration of serum potassium was 4.6 to 5.3 milliequivalents. The only electrocardiographic change that might be related readily to pericarditis in Case 1 was the high, sharp T waves, with the elevated S-T segment, in the chest lead of Oct. 7, 1939. In the electrocardiogram of October 9 the tendency of the T wave to maintain its narrow base is to be noted, as well as the great similarity of the tracings to those of dogs poisoned by potassium (Fig. 1). The absence of the P waves with the maintenance of a regular rhythm could be associated with either auricular standstill or nodal rhythm with the P wave hidden in the QRS complex.

The records in the second case are not as extensive as in the others, but the sequence of defects of conduction which developed in the presence of a high serum potassium is obvious (Fig. 4).

The clinical and laboratory data are most extensive in the third case, and the records are complete over a period of six weeks. It is interesting that the electrocardiograms at first showed developing negativity of the T waves, and it is believed that this may indicate a change toward the patient's usual electrocardiographic pattern, rather than the reverse. During this period the serum potassium had decreased. The electrocardiograms next showed an increase of the voltage of the T waves (Fig. 8), and, concomitantly, the serum potassium increased. Later the electrocardiograms showed the same defects of conduction as in the other two cases.

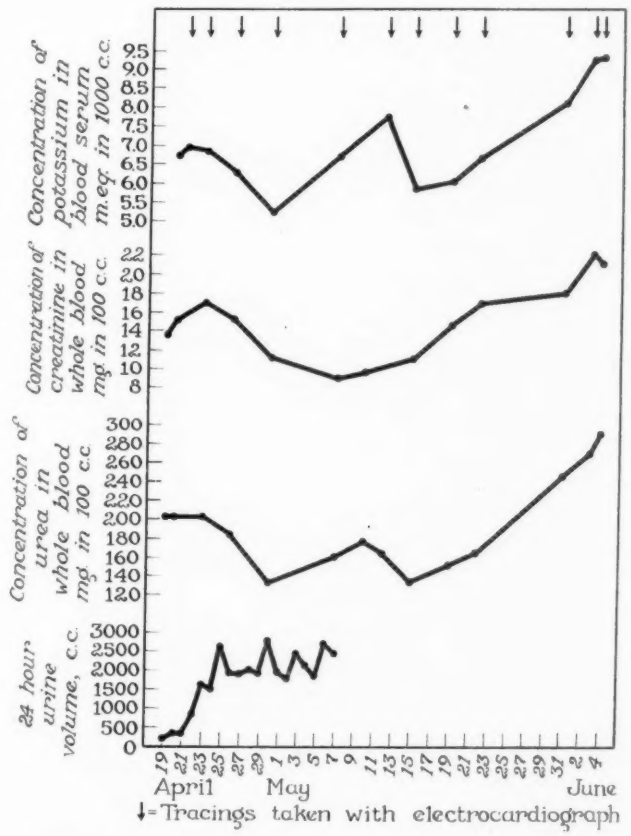

Fig. 13.—Patient 3. Fluctuations of certain constituents of the blood, volumes of urine collected in twenty-four hours, and dates when electrocardiograms were taken during observation in hospital from April 19 to June 4, 1943. Note decrease of blood urea, blood creatinine and serum potassium from April 23 to April 30, and concomitant rise of urinary volume; a steady progressive increase of urea, creatinine, and potassium in the blood from May 15 to June 4.

Premature beats, probably of ventricular origin, were observed in Cases 1 and 2, but not in Case 3. Digitalis was not given to Patient 1, a few small doses were given to Patient 2, and none was given to Patient 3 during the last sixteen days of her life. No potassium salts were administered to Patients 1 and 3.

The final estimation of the concentration of potassium in the blood serum of these patients varied between 8.8 and 10.5 milliequivalents. When, in Cases 1 and 3, the final electrocardiograms and estimations of serum potassium were made, nineteen and thirteen hours before death, respectively, intraventricular block was the striking feature. Finch and Marchand[18] observed similar changes in the electrocardiogram in a case of uremia when the concentration of potassium in the serum was 8.8 milliequivalents. Such changes occurred in the electrocardiograms of both dogs and cats which were given toxic doses of a salt of potassium, at a somewhat higher concentration of serum potassium. In the dog the range was 9.4 to 12, and, in the cat, 7.9 to 14.1 milliequivalents.

It has been demonstrated in both dogs and cats to which large doses of potassium salts have been given that, when intraventricular block has developed, recovery of the heart may occur.[2, 4] Such a recovery was observed by Sharpey-Schafer[19] in a case of aortic stenosis in which the patient ingested 15 to 20 Gm. of potassium salts. Ninety minutes later the concentration of potassium in the serum increased to 9.2 milliequivalents, and intraventricular block was evident in the electrocardiogram. We observed a similar course of events after giving 5 Gm. of potassium bicarbonate to a patient who had chronic nephritis and uremia.[20] The serum potassium of this patient increased in ninety minutes to 9.5 milliequivalents, and early intraventricular block was present in the electrocardiogram. Neither in this case nor in that of Sharpey-Schafer did any untoward symptoms develop, and the widening of the QRS interval subsequently disappeared. Therefore, in the experimental animal and among patients, intraventricular block associated with potassium intoxication is not necessarily an irreversible reaction. However, it should be emphasized that, when recovery from the intraventricular block occurred, the potassium toxemia was temporary, i.e., a matter of a few hours, whereas, in our cases, it was sustained for many hours. Bywaters[8] stated that he gave solutions containing insulin and glucose to a patient who had such an electrocardiogram and a high concentration of serum potassium with beneficial results. In his case severe renal insufficiency had developed after a crush injury to the extremities.

Ventricular fibrillation and death occurred in animals subjected to marked potassium toxemia.[2-4] These events occurred later in sequence than intraventricular block, and when the concentration of potassium in the blood serum was higher—14.7 to 15.8 milliequivalents in the dog and 14.2 to 28.1 milliequivalents in the cat. If death in our cases was due to potassium toxemia, one might suspect that a further rise of serum potassium and ventricular fibrillation occurred subsequent to our final observations. This period was nineteen hours in Case 1 and thirteen hours in Case 3. Finch and Marchand[18] in their Case 1 reported 10.5 milliequivalents of potassium in the serum when ventricular fibrillation and standstill occurred.

The duration of electric systole was disproportionately slightly prolonged in all three cases. In the first case, the Bazett,[21] the systolic index ($QT/\sqrt{cycle}$) varied between 0.40 and 0.44 until the last tracing, when it reached 0.52, which is high. In the second case the systolic index in the first tracing was 0.38, and, in the last tracing, it was 0.43. In the third case the systolic index at the beginning was 0.41. It stayed at about this value for three weeks, then decreased to 0.37 for two tracings, and finally returned to a figure of 0.42 in the tracings taken during the last two days. In this case, in which we have nine electrocardiograms with simultaneous determinations of serum potassium (Table V), there was no direct correlation between the systolic index and serum potassium level. With certain unexplained exceptions there was a good correlation between the height of the T wave (IVR) and the height of the serum potassium (Table V, Fig. 8), a correlation which has been mentioned previously.

TABLE V

ELECTROCARDIOGRAPHIC DATA AND SERUM POTASSIUM OF PATIENT 3

DATE	$QT/\sqrt{CYCLE}$	VARIATION IN VOLTAGE OF T WAVE IN LEAD IVR, MV.	SERUM POTASSIUM, MEQ.
4/21/43	0.41	+0.20	7.0
4/23/43	0.44	+0.28	6.9
4/30/43	0.43	−0.10	5.2
5/ 7/43	0.48	−0.20	6.7
5/12/43	0.45	+0.25	7.8
5/22/43	0.37	+0.15	6.7
5/31/43	0.38	+0.25	8.2
6/ 3/43	0.42	+0.10	9.4
6/ 4/43	0.42	+0.28	9.4

COMMENT

For the last hundred years toxicologists[22] have known that potassium salts, when injected rapidly into the vein of an experimental animal, induce cardiac standstill and death. Since 1938 the subject has been reinvestigated in both the dog and the cat. The results of numerous experiments reveal contemporaneous changes in the blood and electrocardiogram.[2, 4] These alterations are a steady, abnormal increase of the concentration of potassium in the blood serum, and a regular sequence of changes in the electrocardiograms until death from cardiac failure occurs. A similar sequence of events has been observed, also, in experimentally produced uremia.[3] Fortunately, cases of fatal poisoning of human beings after the ingestion or injection of potassium salts have been notably few. In a single instance the concentration of potassium in serum was ascertained and electrocardiographic studies were carried out.[18]

As mentioned in a previous section, Sharpey-Schafer and one of us (N. M. K.)[20] have observed among patients after the ingestion of potassium salts the temporary production of intraventricular block and hy-

perpotassemia. These observations indicate that this stage of intraventricular block, produced by potassium toxemia, can be reversible when the toxemia itself is temporary and reversible. In one case of severe uremia in which the patient did not receive potassium salts, we reported in an earlier paper[1] a sustained, great increase of serum potassium and intraventricular block. Bywaters[8] had a similar experience. Such events were noted also in Case 3 of this series thirty-six hours before death. We think that one may therefore surmise, especially if one remembers what occurs in experimental uremia and in the single case reported by Finch and Marchand,[18] that the period when intraventricular block was evident in our cases was a stage in the sequence before terminal ventricular fibrillation and cardiac death occurred. Further studies nearer the time of death should reveal decisive evidence on this point.

There are several possible reasons why in our three cases the concentration of potassium in the blood serum did not reach as high a level as reported in the dog and the cat: (1) the possibility that the blood specimen may not have been drawn near enough to the time of death; (2) definite previous dysfunction of the myocardium, indicating a possibly diminished tolerance of that organ to potassium; (3) the possibility that, among patients who have uremia, the concentration of potassium in the serum never increases to the same height as it does in animals; for example, a species difference; (4) presence of acidosis in the blood; this was never severe among our patients; (5) changes in the concentration of other electrolytes in the blood serum; for example, increases of sulfate and phosphate, decreases of chloride and sodium; (6) a low concentration of calcium in the serum, suggested by Winkler and his co-workers[23] and by Wood and Moe;[24] this possibility was excluded, at least in Case 3, for the serum calcium was within the normal range; and (7) an increase of toxic nitrogenous metabolites other than the known nitrogenous compounds, such as urea, creatinine, or uric acid.

We believe that there is much circumstantial evidence to support the thesis that the cardiac deaths in our cases were due to potassium toxemia. If subsequent observations confirm such a thesis, it seems clear that the excessive concentration of potassium leads to an abnormal functional disturbance rather than to visible pathologic alterations in the heart. Thus we should have a good example of a disturbance of electrolyte balance leading to a fatal upset of cellular metabolism.

SUMMARY

Serial observations were made in three cases in which severe renal insufficiency and uremia developed. The study included clinical, biochemical, electrocardiographic, and pathologic observations. Consistent observations were a marked increase of the concentration of potassium in the blood serum and the development of an intraventricular conduction defect shortly before death from cardiac failure. These results support the thesis that death in these cases was due to potassium intoxication.

METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

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CONTINUOUS INTRAVENOUS ADMINISTRATION OF HISTAMINE: EFFECT ON THE ELECTROCARDIOGRAM AND SERUM POTASSIUM

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THE effect of histamine on the electrocardiogram has not been studied extensively in man. Because of the increasing clinical use of histamine, further investigation along these lines appears justified and necessary in order to ascertain any heretofore unobserved toxic or permanent effects on the heart.

Schenk[1] was probably the first to study the electrocardiographic changes produced by histamine. He noted frequent ventricular extrasystoles and marked arrhythmia after large doses of histamine given subcutaneously in man.

Massione and Picchio[2] studied electrocardiographically the effects of administering 1 mg. of histamine intramuscularly to nine human subjects. For this they employed the usual three standard leads. They noted an increase in cardiac rate, a decrease in both auricular and ventricular systoles, and an increase in conduction time. They pointed out that histamine should be given only to persons with healthy hearts, for in two cases of myocarditis a distinct increase in auriculoventricular block was seen.

In 1929, Weiss, Robb, and Blumgart[3] used histamine as an agent for measuring the velocity of blood flow, and noted temporary inversion of the T wave in Lead II for some twenty to sixty seconds in a number of their subjects. Later, Weiss, Robb, and Ellis[4] studied the effect of both a single injection and continuous intravenous administration of histamine on Lead II of the electrocardiograms of fifteen persons who had normal cardiovascular systems. Those who were given a single intravenous injection showed progressive depression of the T wave and simultaneous acceleration of the heart rate. With return of the normal cardiac rate, the T wave assumed its original shape. The authors interpreted these changes as produced by the action of histamine on the coronary vessels or on the cardiac musculature. They reported that doses as small as 0.004 mg. per minute may cause a depression of all the complexes of the normal electrocardiogram, but that the effect is most marked on the T wave. With an increase in the dose, the degree of depression was increased until the T wave became inverted. The inversion of the T wave disappeared as the rate returned to normal, "sug-

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gesting that the increase of rate was the result of histamine on the coronary vessels."

Since comparatively little is known concerning the effect of histamine on the electrocardiogram, for only one other group of investigators (Weiss, Robb, and Ellis[4]) have studied the effect of intravenous administration on the electrocardiogram, and they used only Lead II, it was considered worth while to observe further the effect of this substance on all three standard leads and two precordial leads. Also, since the amplitude of the T wave is known to be influenced by abnormal levels of potassium, as has been observed in Addison's disease and in familial periodic paralysis, this study includes the effect of histamine on the serum potassium.

PROCEDURE

Electrocardiograms were made on twenty-five persons before, in the course of, and after the intravenous injection of histamine. These persons were in the horizontal position and in a fasting state. Seven of the twenty-five persons were women and eighteen were men. The ages of the women ranged from 21 to 59 years, with an average age of 35 years, and the ages of the men ranged from 23 to 66 years, with an average age of 45 years. Although these patients cannot be considered entirely normal, none was known to have any significant cardiac symptoms or disease, and each had had a thorough physical examination before treatment with histamine. The diagnoses in these cases included Ménière's syndrome, multiple sclerosis, headaches, arteriovenous fistula, tinnitus, postural vertigo, torticollis, angioneurotic edema of the hands, psychoneurosis, and Parkinson's disease. In eight cases the three standard leads were employed; in seventeen, two additional leads, namely, Leads CR_2 and IVR, were used. Patients who were to receive histamine were allowed to rest for approximately fifteen minutes before the preliminary electrocardiograms were made.

One per cent solution of procaine hydrochloride was used subcutaneously over the site of venous puncture to allay pain and apprehension and to prevent, as much as possible, acceleration of the heart during venous puncture. Continuous intravenous injection of histamine was then started; the rate was slow at first, and then was increased gradually by various increments. In most cases the rate was doubled at each increment. A set of three or four electrocardiograms was made after each increment. The solution contained 2.75 mg. of histamine diphosphate in 250 c.c. of physiologic salt solution. The rates at which it was injected were increased from 0.0017 to 0.044 mg. of histamine base per minute. The 2.75 mg. of histamine diphosphate contains 1 mg. of histamine base. The rates of administration of histamine in this paper are given in terms of histamine base. Nearly all of the patients were given 250 c.c. of the solution containing histamine. Immediately after completion of the intravenous injection, a final set of electrocardiograms was made. Occasionally another set of tracings was taken fifteen minutes later. From six to nine sets of electrocardiograms, consisting of three or four leads each, were made in each case. About five to ten minutes intervened between tracings.

For control, in three of the twenty-five cases further studies were carried out. Electrocardiograms were made in the same manner, but physiologic salt solution, only, was injected instead of the solution con-

taining histamine. In addition to these studies, the concentration of serum potassium was ascertained by the method of Kramer and Tisdall[5] in seventeen cases before and after injection of histamine.

RESULTS

In twenty-four of the twenty-five cases (96 per cent), histamine produced a definite effect on the electrocardiogram. This effect was chiefly loss of amplitude of the T wave. In some cases this loss of amplitude proceeded either to the isoelectric level or to inversion of the T wave in all four leads. The effect was brief. In one case (4 per cent of the twenty-five cases), that of a man, the administration of histamine at high rates failed to produce any effect on the electrocardiogram.

Age.—In order to ascertain the influence of the age of the patient on the changes in the electrocardiogram, the cases were arbitrarily grouped according to the degree and duration of change in the electrocardiograms after the injection of histamine. Four groups were formed. In the first group no changes were found in the electrocardiogram. Only one case fell in this group. In the second group certain slight effects were found. Seven cases were included in this group. All the patients were men, and their average age was 46 years. In the third group moderate changes were noted in the T waves during the administration of histamine, and these changes were present in most instances for a short time after the injection of histamine was discontinued. There were eleven cases in the group. Five of the patients were women and six were men. Their average age was 40 years. In the fourth group the T waves underwent the most marked changes, and, in general, these changes continued longest after the injection of histamine was stopped. Of the six patients in this group, two were women and four were men. The average age of these six patients was 41 years; the youngest patient was 21 years, the oldest, 56 years. Age alone, therefore, did not appear to be a significant factor in the changes in the electrocardiograms after the use of histamine. In all of the cases in group 4, except one, the effect of the drug was prolonged.

Serum Potassium.—The average concentration of potassium before the injection of histamine was 18.8 mg. per 100 c.c. of serum, and after the injection the average concentration was still 18.8 mg. per 100 c.c. In five cases a slight increase followed the injection; in seven, a small average decrease, and, in five, no change followed the injection. The serum potassium seems therefore to have little if any influence on the electrocardiographic complexes and not to be responsible for the changes observed after the injection of histamine.

T Waves.—The predominant effect of histamine seemed to be on the T waves (Table I). The T wave in Lead III most frequently showed the effect of histamine first. The average rate of administration of histamine in milligrams per minute at which the effects were first observed in the various leads is shown in the final column in Table I.

TABLE I

EFFECT OF HISTAMINE ON THE T WAVE

	CASES				AVERAGE RATE OF ADMINISTRATION (MG PER MIN.)
	LOSS OF AMPLITUDE	DEPRESSION TO ISOELECTRIC LEVEL	INVERSION	EFFECT FIRST OBSERVED*	
Lead I	20	2	0	6	0.025
Lead II	20	3	4	11	0.023
Lead III	16†	3	9	14	0.014
Lead CR_2	15	2	1	7	0.024
Lead IVR	12	1	0	6	0.027

*The T waves in more than one lead sometimes show effects at the same time.

†Five subjects already had inverted T waves in this lead, and four had either isoelectric or diphasic T waves in preliminary electrocardiograms.

These figures indicate that the T wave was most easily influenced in Lead III, and least so in Leads IVR and I.

The effect of histamine disappeared immediately after the administration was stopped in nine cases, and, in five other cases, it disappeared in all leads except one. It continued for at least five minutes in five cases, and was back to normal in three cases in ten to fifteen minutes. In only these three cases were electrocardiograms made more than ten minutes after discontinuation of the histamine. These three cases, in which the effect was known to have been lost in ten to fifteen minutes, in addition to the nine cases in which the effect of the drug was lost immediately after injection was discontinued, indicate that the influence of histamine is neither prolonged nor permanent. In two cases, in spite of continued and increased doses of histamine, the T wave recovered its voltage even before the injection of histamine was discontinued (Fig. 1).

One of the greatest effects on the electrocardiogram was produced in the case which follows:

This patient began to show the effect on the T waves of all leads when histamine was injected at the rate of 0.014 mg. per minute. Control electrocardiograms (Fig. 2, *A*) showed left axis deviation and an isoelectric T wave in Lead III. When histamine was injected at a rate of 0.0035 mg. per minute (Fig. 2, *B*), the T waves in Leads I and II began to lose voltage. This effect became more pronounced when the rate of injection of histamine was increased to 0.028 mg. per minute (Fig. 2, *C*). The T wave became isoelectric in Lead I, and inverted in Leads II and III. The T wave in both chest leads also became lower in amplitude. When 0.042 mg. of histamine base was injected per minute (Fig. 2, *D*), the T waves in Lead I and in Leads IVR and CR_2 had regained their former amplitude. In Lead III the T waves remained slightly inverted, but a striking observation in this case, too, was that, instead of a continuous depression of the T wave with increased amounts of histamine, an escape occurred, which was apparently due to some readjustment on the part of the heart, and was manifested by an increase in the amplitude of the T wave. The cardiac rate, however, had not returned to normal. Immediately after discontinuation of the histamine (Fig. 2, *E*), the T waves in Leads I, II, CR_2, and IVR

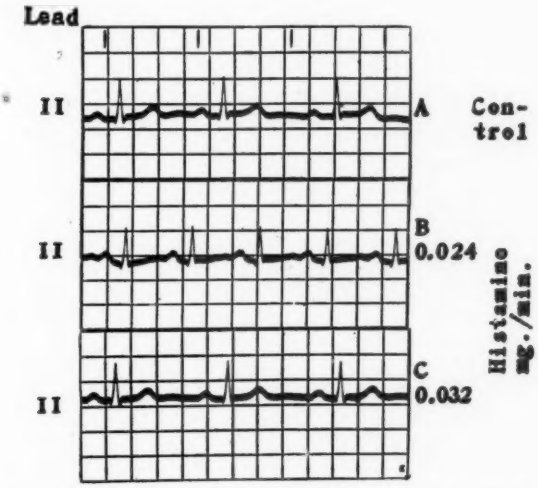

Fig. 1.—Electrocardiograms. *A*, Control; *B*, isoelectric T wave nine minutes after *A*; *C*, increase in T-wave amplitude ten minutes after *A*, in spite of continued and increased rate of administration of histamine.

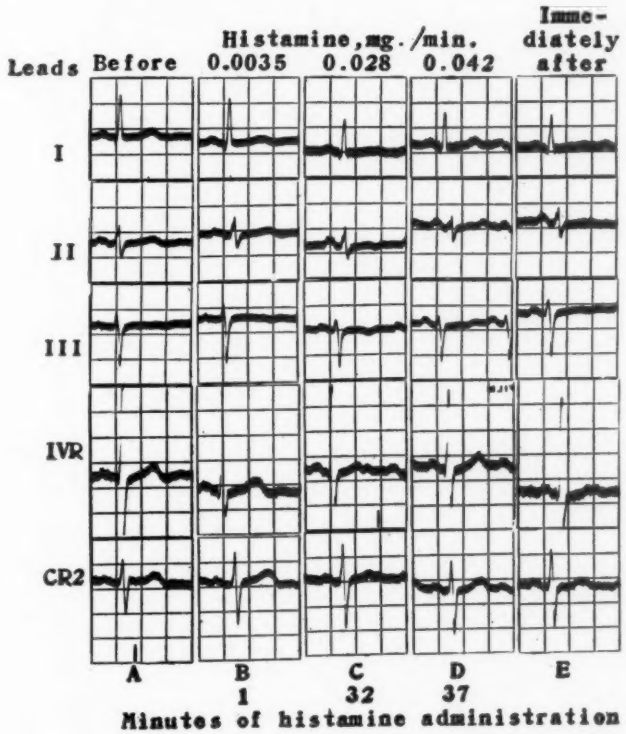

Fig. 2.—Electrocardiograms efbore, in the course of, and after administration of histamine. *A*, Control observation shows left axis deviation and isoelectric T wave in Lead III; *B*, T waves in Leads I and II are flattened slightly; *C*, T waves are isoelectric in Lead I, inverted in Leads II and III, and of lower amplitude in both chest leads; *D*, T waves have regained their amplitude in Lead I and some of their amplitude in both chest leads. In Lead III they are still slightly inverted; *E*, T waves in Leads I and II and both chest leads are flattened again.

appeared flattened again. On review of all of the electrocardiograms, it appeared as if the right side of the heart had become overburdened temporarily, as shown by the inverted T waves in Leads II and III, then had readjusted itself to the added strain in spite of the increased and continued dose of histamine. With the higher rates of injection of histamine, periods of overactivity of the heart, lasting three to four minutes, were observed with each increment of dosage. Also, the patient's respirations became more rapid and deep. Abnormal exchange of gas by hyperventilation, in addition to right ventricular strain, is a possible factor in the production of changes in the electrocardiograms.

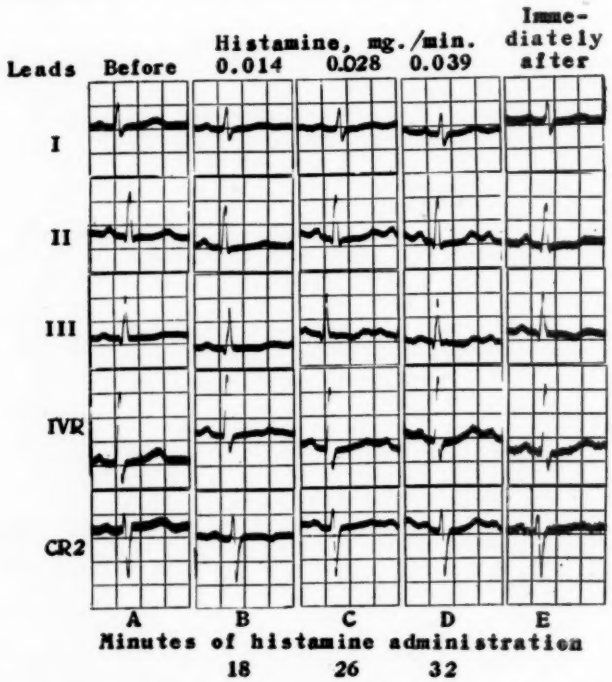

Fig. 3.—Electrocardiograms before, in the course of, and after administration of histamine. *A*, Control, showing isoelectric T waves in Lead III; *B*, T waves are decreased in all leads, flattened in Leads I and II, diphasic in Lead III, positive, but notched, in Lead IV R, and inverted in CR_2; *C*, T waves in Lead I and both chest leads are of low amplitude, and in Lead III are inverted; the inversion of the T wave in Lead CR_2 which was present in *B* has disappeared; *D*, T waves in Lead III are diphasic, and in both chest leads are increased in amplitude; *E*, T waves of all leads are of low amplitude; those in Lead CR_2 are most diminished.

Left axis deviation, in this case as well as in three others, remained unaltered throughout all of the tracings before, during, and after administration of histamine. Small Q waves were observed in Lead IVR at rates of administration of histamine base of from 0.009 to 0.028 mg. per minute.

In another case (Fig. 3), inversion of the T wave in Lead CR_2 and the presence of a notched, positive T wave in Lead IVR indicated right ventricular strain as well as in any of the cases studied. This case was the only one in which the T wave was inverted in any of the chest leads.

In the control electrocardiogram (Fig. 3, *A*), isoelectric T waves were noted in Lead III. When histamine was being given at the rate of 0.014 mg. per minute, the amplitude of the T waves was decreased in all leads, flattened in Leads I and II, diphasic in Lead III, and inverted in CR_2 (Fig. 3, *B*). The T wave in Lead IVR was a notched, positive wave. The maximal effect was observed when histamine base was being injected at the rate of 0.028 mg. per minute (Fig. 3, *C*). The T wave in Lead I at that time still exhibited low amplitude; in Lead III it was still inverted, but the inversion had disappeared in Lead CR_2. The T waves in both chest leads were still at low amplitude. When the rate of injection was 0.039 mg. of histamine base per minute (Fig. 3, *D*), the T wave in all leads regained considerable amplitude, and that in Lead III had become diphasic. Immediately after completion of the intravenous injection (Fig. 3 *E*), the T wave in Lead III became inverted again, whereas those in both chest leads lost what amplitude they had gained during the maximal rate of injection. In Lead I the T wave regained its original amplitude, but the remaining leads showed diminished voltage of the T waves. In this case the effect of histamine on the electrocardiogram was great, but the subjective and objective effects were slight. Electrocardiograms showed a Q-T time of 0.40 second in Lead II when the rate of administration of histamine was 0.039 mg. per minute; this is definitely prolonged when compared to the normals of Bazett. In the remaining twenty-two positive cases, similar, but less pronounced, electrocardiographic changes were exhibited.

Other Electrocardiographic Observations.—Premature ventricular contractions were observed after the administration of histamine in four cases. They usually developed when histamine was given at rapid rates, but in one case they disappeared at high rates, although they were present in all preliminary tracings. One patient had incomplete bundle branch block (QRS interval of 0.12 second) which was unknown to any of us until later. However, the incomplete bundle branch block did not change with the various rates of administration of histamine, nor did the patient appear to suffer in any way from the injection. Two and a half years later, electrocardiograms did not reveal any further change in this incomplete bundle branch block.

Notching of the P wave in Leads II and III disappeared in two cases during the injection of histamine. In three cases, however, diphasic P waves in Lead III, notched P waves in Leads II and III, and diphasic P waves in Leads I and III remained unchanged throughout all tracings. In one case the notched P wave returned after discontinuation of the injection of histamine. A P wave of low amplitude in Lead I became higher with increased flow of histamine in another case. In one case, the P waves in Leads II and III were notched occasionally during the administration of histamine. Notching and slurring of the QRS complex was not changed by histamine in thirteen cases. Notching was frequently observed in Lead III, and the slurring was about equally

distributed in Leads I, II, and III. Loss of voltage of the QRS complex was not striking nor consistently present. Diminution of the S wave in Lead IVR was observed in two cases. This effect appeared in both cases when histamine was being given at a rate of 0.0017 to 0.0035 mg. per minute, and continued until after the injection was completed.

Left axis deviation was encountered in six cases. It was present throughout all tracings in four cases, but in one it was found only immediately after administration of the drug was discontinued. In the remaining case, the slight left axis deviation which was present on the initial examination disappeared when the rate of histamine administration reached 0.022 mg. per minute. It had not reappeared approximately six minutes after discontinuation of injection of the drug. In this case also, premature ventricular contractions disappeared with high dosages of the drug. No cases of right axis deviation were encountered.

The T waves in Lead III which were already inverted in preliminary tracings were not deepened with increased amounts of histamine. In two cases the T waves in Lead III which were inverted became diphasic on increased rates of administration of histamine.

The cardiac rate was increased by the administration of histamine, as illustrated by Fig. 4. Little effect was noted until a rate of 0.013 and 0.015 mg. per minute was reached. Then, with each increment in dosage, there was a corresponding rise in cardiac rate. Sinus tachycardia was usually present with maximal administration. When the administration of the drug was stopped, the heart rate dropped back to its original, or to a lower, rate within five to ten minutes. The cardiac rhythm shifted back to either sinus rhythm or sinus bradycardia. The difference in the number of cases above the various rates of administration, as shown in Fig. 4, is explained by the fact that in some cases histamine was injected at different rates than in others. This was done because ability to tolerate the drug without headache varied. Some patients could take it rapidly, as if it were only physiologic salt solution, whereas others were more sensitive.

The electrocardiographic cycle was analyzed in order to find out what part of the cycle was affected. In thirteen cases during maximal injection of histamine there was an average decrease of 0.034 second in the P-R interval, as compared to the control period. In ten cases the P-R interval did not change, and in one case it increased temporarily. In this case the P-R interval increased from 0.20 to 0.24 second when the rate of administration of histamine increased from 0.0017 to 0.0158 mg. per minute. With increasing rates of injection, however, the P-R interval returned to its original length, namely, 0.20 second. In one other case the P-R interval was prolonged initially to 0.24 second. However, at rates of histamine injection from 0.021 to 0.044 mg. per minute, the P-R interval was reduced to between 0.20 and 0.22 second. Immediately after discontinuation of the injection of histamine the P-R

interval returned to its former length of 0.24 second. Failure to observe impairment of auriculoventricular conduction, as reported by other investigators, may have been due to the relatively smaller amounts of histamine used. There was no effect on the QRS interval. The S-T interval decreased in twelve cases, remained unchanged in ten, and increased in three. The average decrease in time was approximately 0.05 second. The average increase was 0.027 second. The Q-T time was observed to be prolonged in eight cases when the cardiac rate was elevated by the histamine, that is, the Q-T interval remained what it was originally, and did not decrease with the increase in cardiac rate. Compared to the normal values of Bazett, the average decrease in Q-T time would have been 0.072 second, but actually the average was 0.0075 second. The T-P interval, of course, showed an inverse proportion to the increase in cardiac rate, and was reduced to zero in some cases.

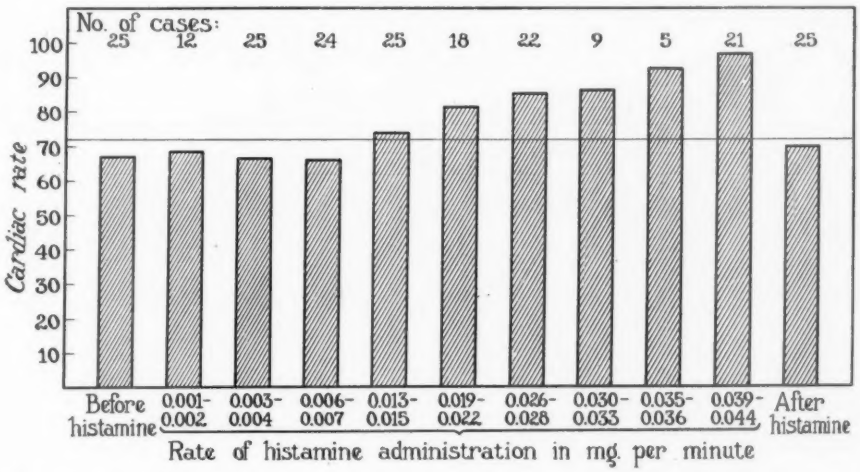

Fig. 4.—Increase in heart rate in proportion to rate of administration and dose of histamine.

COMMENT

To explain how histamine causes the T wave to lose amplitude and become inverted is a difficult undertaking, for it involves the theory of electrocardiography and the mechanism of formation of the T wave, concerning which investigators are not all agreed. Therefore, although an attempt on our part to explain this effect on the T wave may appear presumptive, it is done only for the purpose of presenting what seems to be the most plausible explanation in the light of the present investigation.

Several possibilities may be considered in regard to the manner in which histamine produces its effect on the T wave. The first is whether the amine produces coronary vasoconstriction and thereby brings about myocardial ischemia. There are several pieces of evidence against this explanation, for such experimental work as that of Essex, Wegria, Herrick, and Mann[6] on the trained dog and the work of Anrep[7] on the heart-

lung preparation of human beings demonstrate that histamine produces coronary vasodilatation in these species. Moreover, in the twenty-five cases investigated and many others not included in our study, neither anginal distress nor signs of coronary insufficiency were encountered. Also, if anoxemia were produced, the electrocardiographic changes which are characteristic of this condition, as shown by Levy, Bruenn, and Russell,[8] would be expected. Inversion of the T waves in Leads I and IVR was never encountered, nor was the RS-T junction displaced, as they reported. Loss of voltage in the QRS complex was not observed, either. However, Levy, Bruenn, and Russell[8] mentioned that, in normal persons during induced anoxemia, the T waves tended to lose amplitude in all four leads, and inversion of the T waves in Leads II and III occasionally occurred. Rothschild and Kissin[9] pointed out that the alterations of the electrocardiograms in anoxia disappear slowly, and persist in diminishing degrees in some instances for as long as thirty minutes. The work of Levy and his associates and of Rothschild and Kissin is of particular importance because it demonstrates that the electrocardiographic changes caused by anoxia, although they are similar in some respects to those produced by histamine, are, in the main, different.

The next question is whether histamine produces its effect on the T wave through the vagus nerve. Stimulation of the vagus has been shown to produce T waves of low amplitude by Samojloff,[10] Rothberger and Winterberg,[11] and Kronenberger and Ruffin.[12] This question can be answered in the negative if the work of Hashimoto,[13] who sectioned the vagal nerves of dogs and also gave large enough doses of atropine to paralyze the vagal nerves, is accepted. He found that the effect of histamine on the heart was not prevented by such procedures, and concluded that the action of histamine was mediated in some other manner. Moreover, histamine always produces acceleration of the heart, which is not a characteristic of vagal activity.

Whether histamine produces its effect on the T wave through the sympathetic nervous system must also be considered. This is hardly likely, for stimulation of the accelerator nerves, as shown by various investigators,[10-12] the use of epinephrine, and conditions, such as hypoglycemia, which cause an increased outflow of epinephrine, have produced larger than normal T waves.

The next question to be considered is whether the amine acts directly on the myocardium as a toxic agent. If this were true, the faster histamine is administered, the more pronounced would be the loss of amplitude of the T wave and the deeper the inversion. This is not entirely true. In several cases the amplitude of the T wave returned to normal in spite of continued and increased administration of histamine. However, histamine may act directly on the myocardium.

The most likely explanation of the T wave negativity is that it reflects right ventricular strain, although tachycardia and hyperventila-

tion may be additional factors. Although the electrocardiographic changes do not resemble those in pulmonary embolism exactly, because there is no prolongation of the Q wave in Lead III or incidence of right axis deviation, in one case the T wave was inverted in Lead CR_2 and was notched and positive in Lead IVR. This probably represents the maximal effect of histamine in producing right ventricular preponderance, for, in the other cases, the effect was much less pronounced. Dale and Laidlaw[14] reported that large intravenous injections of histamine produced transient distention of the right side of the heart, with weak right ventricular contractions, in cats which were given artificial respiration while the thorax was open. Also, Kirch[15] reported that, in the dog, cat, rabbit, and guinea pig, a definite tonogenic dilatation of the right ventricle occurred when histamine was injected into the veins and heart. Daily injections produced a definite right-sided hypertrophy of the heart in the dog and cat. This was believed to be due to an increase in the blood pressure in the pulmonary circulation, caused by contraction of the small pulmonary veins, aided by spasm of the bronchial musculature. The results of our investigation bear out the possibility that increased intrapulmonic pressure is responsible for the electrocardiographic changes, as shown by the preponderance of inversion of the T waves in Leads II and III, as well as the case in which the T wave was inverted in Lead CR_2, with a positive, notched T wave in Lead IVR. These changes point to right ventricular strain as probably the most plausible answer.

The effect of histamine was not prolonged, which indicates that it was being quickly neutralized or destroyed in the blood stream. Prolongation of the conduction time was found in only one case. In most of the cases the conduction time, contrary to experimental reports in the literature, was decreased. As a whole, the electrocardiographic changes did not appear remarkably significant, and were of a transient and physiologic nature. Experimental work which substantiates this opinion is that of Ettinger, Hall, and Lang,[16] who gave dogs histamine intravenously daily for as long as 266 days. The concentration of the histamine solution was 1:10,000, and 2 to 4 c.c. were given per minute for ninety minutes daily; this was enough to double or triple the heart rate. Post-mortem examinations revealed no evidence of degenerative changes in the coronary arteries or myocardium after the conclusion of the experiment. In our experience, histamine has never precipitated an attack of angina pectoris or coronary occlusion, either in the twenty-five cases studied or in many hundred other cases in which histamine was given intravenously. From this it might be inferred that histamine does not produce coronary vasoconstriction.

In the concentration used, and under the conditions set forth in this paper, the electrocardiographic changes induced by histamine appear to be physiologic and relatively unimportant. Therapeutically, the importance of such a conclusion is evident, but a word of warning should

be voiced for patients who have chronic asthma, for they are notoriously sensitive to histamine.

SUMMARY AND CONCLUSIONS

Electrocardiograms were made on twenty-five human subjects: seven women and eighteen men who did not have cardiac disease. These electrocardiograms were made before, in the course of, and after the continuous intravenous administration of 2.75 mg. of histamine diphosphate in 250 c.c. of physiologic salt solution at rates varying from 0.0017 to 0.044 mg. per minute. Physiologic salt solution was given intravenously to three patients in the same manner as histamine diphosphate, and did not have any effect on the electrocardiograms in any of the four standard leads. Electrocardiograms were taken with the usual three leads in eight cases, and with the aid of Leads CR_2 and IVR in the remaining seventeen cases.

Age and concentration of serum potassium appeared to play little, if any, role in the electrocardiographic changes which occurred after the intravenous use of histamine.

Significant changes were observed in the electrocardiograms in twenty-four of the twenty-five cases (96 per cent). The most common change was loss of amplitude of the T waves in different leads, sometimes in all leads, which, in some cases, proceeded to either the isoelectric level or to inversion of the wave. The first effect appeared most frequently in Lead III, next in Lead II, then in Lead CR_2, Lead I, and finally in Lead IVR. Inversion of the T waves was observed in four cases in Lead II, in nine cases in Lead III, and in one case in Lead CR_2. No inversion was observed in Leads I and IVR. The effect of histamine on the T waves disappeared within five to fifteen minutes after injection of the drug was discontinued. The extent of loss of T-wave voltage was roughly and directly parallel to the rate of administration of histamine. In some cases, however, the effect of histamine was lost, and the T waves recovered either partially or completely their former amplitude in spite of a continued and sometimes increased dosage of histamine.

The cardiac rate was increased, on an average, 26 beats per minute by the administration of histamine. The average rate before injection was 68 beats per minute, and, during maximal injection of histamine, 94 beats per minute. The cardiac rhythm was also affected; the initial rhythm was usually sinus arrhythmia, sinus bradycardia, or sinus rhythm, which shifted to sinus tachycardia during maximal rates of injection.

Impairment in atrioventricular conduction was manifest in only one case, and this was for only a short time during the early stages of the injection of histamine. In all other cases the P-R interval or the conduction time decreased. In one case of incomplete bundle branch block, no further impairment in conduction followed the use of histamine.

Premature ventricular contractions were observed after the administration of histamine in four cases. They usually developed during high rates of injection. Flattening of the QRS complex was not striking nor consistently present.

Left axis deviation was observed in six cases and was present throughout all tracings in four cases. In one of the other two cases, left ventricular preponderance appeared after the injection of histamine, and, in the other, disappeared with increased doses of histamine. Right axis deviation was not encountered.

Electrocardiographically, the effects of administering histamine intravenously in man, in the manner described, may be considered of minor physiologic importance. No clinical or electrocardiographic evidence of permanent cardiac damage was observed in any of the twenty-five patients. No anginal distress or definite symptoms of coronary insufficiency were observed.

The authors wish to thank Dr. A. R. Barnes for criticism and suggestions.

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Clinical Report

BALL THROMBUS IN THE RIGHT AURICLE OF THE HEART, WITH A DESCRIPTION OF THE SYMPTOMS PRODUCED

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A CASE of ball thrombus of the right auricle of the heart is reported for the following reasons:

1. A review of the literature revealed only thirty-five authentic cases of ball thrombus of the heart. In thirty-four of these the ball thrombus was found in the *left* auricle. The single exception was found in the right ventricle.[1] The case herein presented, therefore, represents the first reported instance in which an unquestionable ball thrombus occurred in the right auricle.

2. The presence of the large, freely movable ball in the right auricle produced an unusual syndrome that may lead to a consideration of this possibility in other cases. The diagnosis of a ball thrombus of the left side of the heart has been rarely made or even suggested ante mortem. So far as we can ascertain, it has never been made and confirmed in relationship to the right auricle. In this case an unusual series of findings made it possible to deduce that a movable thrombus was acting as a ball valve over the tricuspid orifice, although it could not be ascertained whether it was loosely attached or entirely free.

3. Lastly, the ball thrombus was of unusual size, measuring 6.8 cm. in diameter, whereas, in the previously reported cases, the thrombi varied from 1 to 4 cm.

Certain criteria, set down by Welch, in 1899,[2] have been generally acknowledged as necessary of fulfillment before the anatomic diagnosis of a ball thrombus can be accepted. There must be (a) entire absence of attachment, with consequent free mobility, (b) imprisonment in consequence of excess in diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it, (c) such consistency and shape that the thrombus must not of necessity lodge as an embolus in this passage. Our case clearly fulfills these specifications.

No attempt will be made to review all of the reported cases of ball thrombus of the heart. The first case reported, a ball thrombus in the left auricle, was described by William Wood, of Edinburgh, in 1814.[3] Nearly seventy years later, von Recklinghausen[4] described his cases.

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He is nevertheless frequently referred to in the German literature as the original observer of this phenomenon. Abramson[5] ably reviewed the literature up to 1924. Since that time others have added cases.[6-15]

Only a single case in the literature needs to be considered in relation to the one here presented. This was reported by MacLeod, in 1882.[16] Recklinghausen,[4] Strange,[17] and Abramson[5] concluded that this case should not be admitted to the class of ball thrombi. While the possibility that MacLeod did find a true ball thrombus does exist, it cannot be clearly so classified from his report because of failure to describe certain essential structural features. These are: the presence or absence of a pedicle, the exact shape of the "clot," and its size relative to that of the tricuspid orifice. MacLeod's exact description was as follows: "In the right auricle was a very firm almost cartilagenous grayish yellow, movable clot, half as large again as a walnut lying over the tricuspid orifice."

Extreme air hunger in the absence of any evidence of interference with the air passages, and with free expansion of the chest, together with periodic unconsciousness and a very thready pulse, led MacLeod to conclude that "there was some interference with the afflux of blood to the lung. The signs and suddenness of the attack pointed to a large embolic plug in the lesser circulation somewhere near the right side of the heart and probably in the pulmonary artery." These deductions did not include the possibility of a ball thrombus in the right side of the heart.

REPORT OF CASE

The patient, a 47-year-old, white, married man, was admitted Jan. 7, 1943, to the Army and Navy General Hospital because of acute heart failure. He had been in good health until the age of 23 years (1919), when he fainted several times while taking exercises. He stated that he was discharged from the Army because of these fainting spells. From that time he experienced increasingly severe dyspnea, as well as subjective evidences of cardiac insufficiency on exertion. On Aug. 4, 1939, he was hospitalized because of signs of a mild degree of cardiac decompensation; this quickly cleared up, and he left the hospital in relatively good health. On Aug. 18, 1942, he experienced his first definite and severe attack of cardiac decompensation. He was then hospitalized, and had severe dyspnea, cough, abdominal swelling, and edema of the ankles. The diagnosis made at that time, according to his statement, was "valvular heart disease." No irregularity in cardiac rhythm was noted. He responded to rest in bed and digitalization with marked improvement. A chest roentgenogram, taken Aug. 28, 1942, revealed an enlarged heart, with marked prominence of the right auricular border (Fig. 1). He left the hospital Sept. 26, 1942, but returned Oct. 6, 1942, with a second severe break in compensation. While at home he had failed to maintain digitalization and had consistently exceeded his exercise tolerance. During this admission he came under the observation of the present authors. This attack was characterized by the following symptoms: severe dyspnea, with orthopnea, severe precordial pain, cough, nausea, oliguria, and weakness. Physical examination revealed an acutely distressed, dyspneic patient with a dusky purplish cyanosis

of the face. The veins of the neck were engorged and actively pulsating. The timing of this pulsation was difficult. Diffuse, fine, persistent, crepitant râles were heard posteriorly over the bases of both lungs. These were not moist. The heart was enlarged, on percussion, to the left anterior axillary line in the sixth intercostal space. In this area a diffuse apical pulsation was visible and palpable. The right side of the heart extended approximately 6 cm. to the right of the midsternal line at the same level. The base was not widened. The rhythm was totally irregular. This was interpreted as due to auricular fibrillation, which was confirmed by the electrocardiogram. Rough systolic and soft blowing diastolic murmurs were heard, and were loudest over the mitral area. These were audible from the right border of the sternum to the left apex. The abdomen appeared to be enlarged due to moderate ascites. There was a large tender liver that extended 4 finger-breadths below the costal margin. The liver pulsated synchronously with the ventricular systole. There was moderate edema of the ankles. Roentgenograms taken during this admission showed essentially the same picture of the heart as that seen during the first admission. Other laboratory data were essentially irrelevant.

The patient again responded rather remarkably to rest in bed and digitalization. His symptoms were definitely improved, although his auricular fibrillation continued and his exercise tolerance remained very limited (e.g., walking slowly across a room). The cyanosis, as well as the engorgement and pulsation of the veins of the neck, was markedly lessened. The liver decreased in size to within normal limits and ceased to pulsate. He left the hospital on Nov. 14, 1942, against medical advice. The diagnoses at the time of discharge from his second admission were as follows:

1. Rheumatic fever, inactive.
2. Myocardial degeneration with insufficiency, secondary to No. 1.
3. Mitral stenosis and insufficiency, secondary to No. 1.
4. Tricuspid insufficiency, secondary to No. 1 and No. 3 (possible tricuspid stenosis?).
5. Cardiac hypertrophy and dilatation affecting all chambers, secondary to No. 1, No. 2, No. 3, and No. 4.
6. Cardiac arrhythmia, severe, chronic, with auricular fibrillation and ventricular premature contractions, secondary to No. 1 and No. 2.

He was advised to continue a maintenance dose of digitalis, but his personal physician discontinued this and replaced it with strychnine. When he became more decompensated, digitalis was again used, but it was rather irregularly taken, and he had none during the two days prior to his final admission on Jan. 7, 1943. On this admission he was again in an extreme state of decompensation. The symptoms and signs were essentially as they were on the second admission. Nausea, dyspnea, orthopnea, ascites, and oliguria were, however, somewhat more prominent than previously. The dyspnea appeared to be of an oxygen hunger type, and not due to respiratory obstruction or congestion. There was no pain in the chest. He gave the history that, on several occasions during the preceding month, his left leg became limp when he tried to walk. This was not accompanied by pain or swelling of the leg.

On his last admission (Jan. 7, 1943) the physical signs relating to the heart were as follows: There was a diffuse visible pulsation in the

area of the fifth and sixth intercostal spaces and at the left anterior axillary line. The rhythm was still totally irregular—the apical rate approximated 140 per minute, with a deficit at the radial artery of 10 to 20 beats. The rough systolic and soft, blowing, diastolic murmurs above described were heard from the right border of the sternum to the left axilla at the level of the sixth intercostal space. They appeared to be loudest to the left of the sternum. The dusky cyanosis of the face and neck was pronounced, and systolic pulsations of the cervical veins and of the markedly enlarged liver were very striking. The right sub-

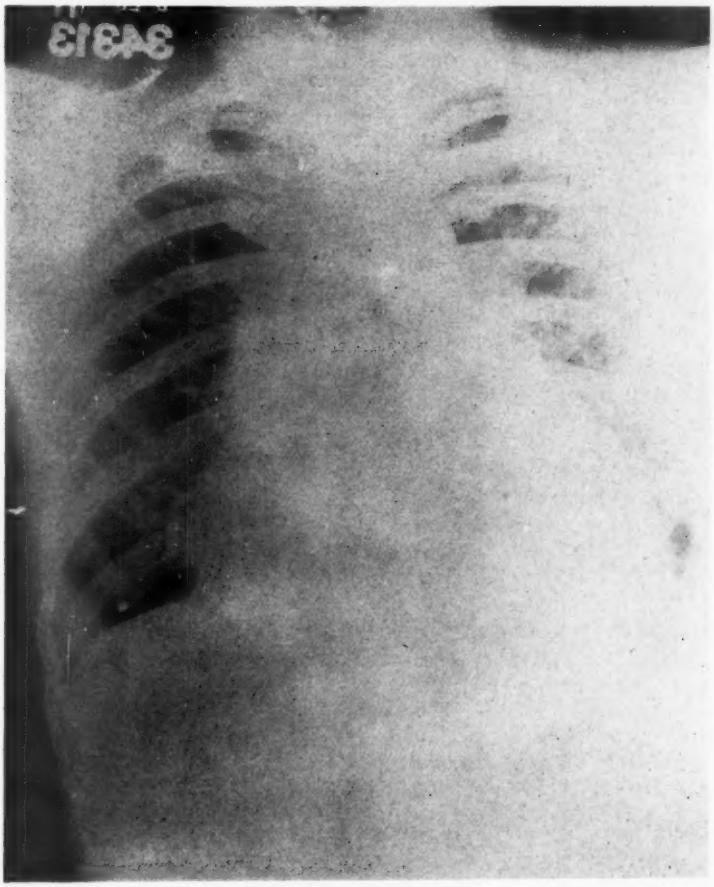


Fig. 1.—Roentgenogram of chest taken Aug. 28, 1942, showing marked generalized enlargement of the heart, with especial prominence of the right auricular area.

clavian vein was distended, showing behind and above the right clavicle. At times, during an acute attack, the saphenous veins were noted to pulsate, but this was not constant. Slight pretibial edema was present, and he had generalized peripheral arteriosclerosis.

Laboratory Data.—On admission the urine had a specific gravity of 1.015. It contained no sugar, but 1 plus albuminuria was present. Microscopically, 10 to 15 leucocytes and a few hyaline and granular casts per high-power field were seen. Increased amounts of albumin and hyaline and granular casts were noted terminally. The blood Kahn

TABLE I

LABORATORY STUDIES

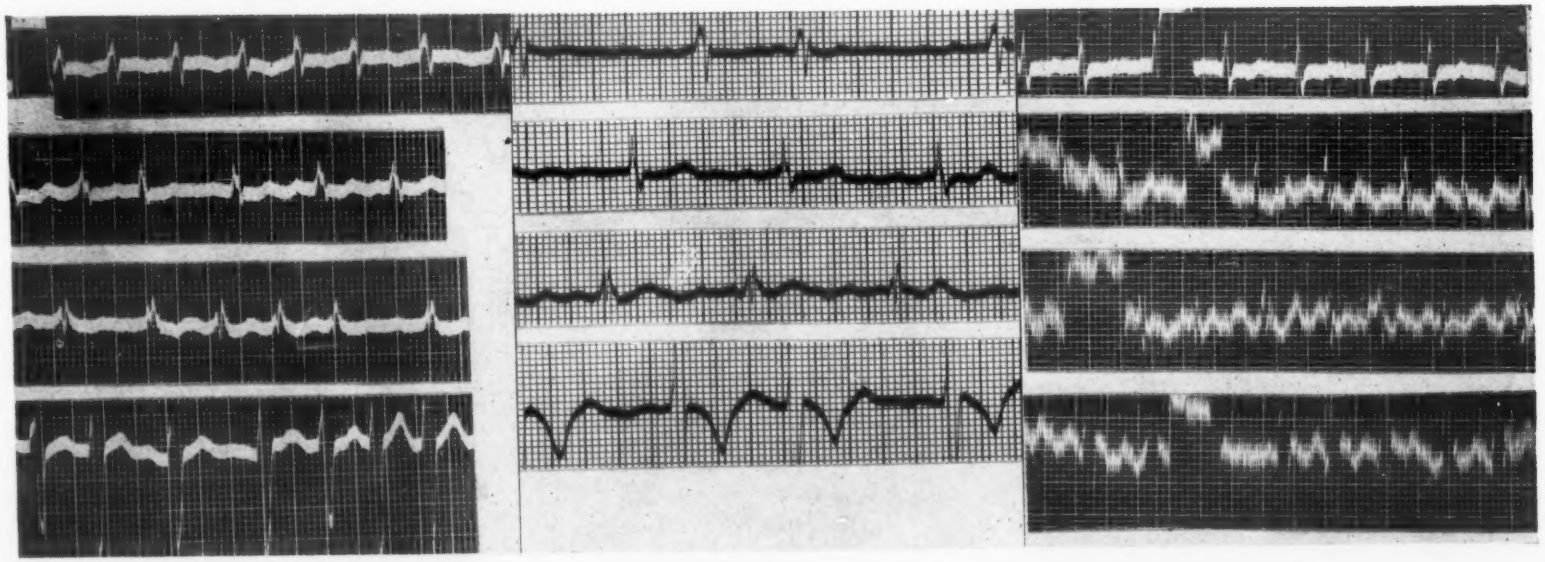
	1/11/43	1/14/43	1/18/43	2/25/43
Blood Nonprotein Nitrogen	85 mg. %	76 mg. %	42 mg. %	300 mg. %
Blood Creatinine	3.15	3.0	2.27	5.0
Blood Sugar	142.8		83.3	222.0
Blood chlorides				672.0

	1/9/43	1/15/43	2/25/43
R.B.C.	3,930,000	4,610,000	4,710,000
W.B.C.	15,300	7,200	50,000
Hgb.	80%	95%	98%
Polymorphs	82%	76%	88%
Lymphocytes	18%	24%	12%
Polychromatophilia			
Occasional normoblasts			

test was negative. An electrocardiogram taken on admission, Jan. 7, 1943, showed auricular fibrillation with a ventricular rate of 140, with slurred QRS complexes of low amplitude in Leads I, II, and III. A diphasic T_2 and inverted T waves in Lead III were noted. There was no evidence of a digitalis effect (Fig. 2*A*).

Hospital Course.—He was immediately put to bed and given sedatives, ammonium chloride, theobromine, and digitalis, and his fluid intake was restricted to 1,200 c.c. daily. The blood pressure was approximately 100/90. During the next forty-eight hours his condition became progressively worse; nausea and vomiting permitted the use of only parenteral medication and feeding. Oxygen was administered continuously through a catheter in the nose, and 2 c.c. of mercupurin were given. The ventricular rate varied between 140 and 160. By the third day (Jan. 10, 1943), his condition had improved slightly. His ventricular rate had slowed to 95 and the electrocardiogram showed early evidence of a digitalis effect. He appeared more comfortable. The liver had receded from 4 to 2 fingerbreadths below the costal margin. His fluid output had markedly increased, but unfortunately was not recorded. The following day (Jan. 11, 1943), his general condition was further improved. The edge of the liver was barely palpable, and the hepatic and venous pulsations were markedly reduced. The patient appeared somewhat drowsy and slightly dehydrated, so that his fluid intake was increased to 1,500 c.c. The administration of oxygen by nasal catheter was continued. The ventricular rate averaged between 90 and 100. From this time, digitalization was maintained by the use of 1½ grains (0.1 Gm.) once or twice a day. This was occasionally supplemented by one ampoule of digifoline. The condition of the patient, evidence of failure, ventricular rate, and frequent electrocardiographic records determined the dosage.

On Jan. 12 he was still drowsy and unaware of his surroundings. The most striking change was the disappearance of all abnormal venous pulsation. The edge of the liver was no longer palpable. The blood pressure was 110/70. The ascites and edema had disappeared. Oxygen was still being administered continuously. The next day (January 13) he appeared much better, and was fairly alert for the first time. The liver was not palpable and the abnormal venous pulsations were still absent. The ventricular rate was approximately 100. The cardiac rhythm was auricular fibrillation, with a few ventricular premature contractions. On January 14 the patient appeared further improved.



A. *B.* *C.*

Fig. 2*A*.—Jan. 7, 1943. Ventricular rate about 140. Auricular fibrillation. QRS complexes 0.08 second duration. QRS slurred and notched, all leads. Diphasic T_1, and negative T waves, Lead III. No digitalis effects.

Fig. 2*B*.—Jan. 19, 1943. Ventricular rate 68. Auricular fibrillation. QRS complexes 0.12 second duration. QRS complexes slurred and notched. Diphasic T waves, Lead I; inverted T waves, Lead V_4.

Fig. 2*C*.—Feb. 25, 1943 (patient in extremis). Ventricular rate about 150. Auricular fibrillation. QRS complexes 0.08 second duration. RS-T segments depressed, Lead I; diphasic T waves, Lead I.

He was no longer cyanotic, and oxygen was discontinued. During the next nine days he made slow but steady progress. His heart remained quite well compensated on a dose of 0.1 Gm. of digitalis daily. His cardiac rate averaged about 66 (Fig. 2*B*). His mental condition was now good. His blood pressure averaged 100/70. Within twenty-four hours, however (Jan. 27, 1943), and without any change in the treatment, he again showed evidence of tricuspid insufficiency. The liver once more became markedly enlarged and pulsatile, and the veins of the neck engorged. The ventricular rate suddenly dropped to 46. The possibility of overdigitalization was considered, and the dose was reduced to 0.032 Gm. (½ grain) daily. Mercupurin (1 ampoule) was given parenterally. Once more, over a period of seven days, his condition showed steady improvement. He felt much better, but the signs of tricuspid insufficiency remained (pulsating liver and veins, and cyanosis). This relatively comfortable phase continued another week, until Feb. 14, 1943, when he apparently had an acute cerebral accident. He developed flaccid paralysis of the entire left side of the body. The head, neck, mouth, and eyes were drawn to the right. The blood pressure was approximately 150/80-60. The next day (Feb. 15, 1943), flaccid paralysis of the left side was still present. A Babinski sign had developed on the left side, but there was none on the right. The asymmetry of the face was less marked. He could hold his head more toward the midline. The tongue could be held nearly straight. The eyes, however, could not be rotated to the left. He reacted to abdominal palpation as if he had generalized pain. At this time the liver and neck veins had again receded, and there was no shortness of breath. It was believed that he had probably had a cerebral embolism from a left auricular thrombus. During the next ten days there was very little change in the neurological signs. Fever developed on February 20, and the temperature reached 105° F. Sulfathiazole was given, and the temperature returned to normal, but rose again to 102° F. terminally. The evidences of tricuspid insufficiency again returned to a marked degree and increased steadily until Feb. 24, 1943, when they reached a maximum; scattered coarse râles were heard throughout the bases of both lungs. A roentgenogram of the chest taken at that time showed evidence of moderate pulmonary congestion and marked enlargement of the heart to the left and to the right, with prominence of the right auricular border (Fig. 3). This was not remarkably different from the one taken Aug. 28, 1942 (Fig. 1). Within twenty-four hours, however, a very striking phenomenon took place. As shown in Fig. 4, the roentgenogram taken February 25 showed a marked reduction in the total size of the heart. Especially noteworthy was the total disappearance of the right border behind the sternal shadow. This was once more accompanied by a disappearance of the liver under the costal margin, and absence of abnormal pulsations of the cervical veins. This series of rapid changes in the severity of the tricuspid syndrome, together with the sudden reduction in the size of the right side of the heart, led the clinicians to conclude that a large thrombus must be riding over the tricuspid valve and exerting a ball valve action. There was no way of determining whether it was attached by a pedicle or was a free, ball thrombus. In either case the action could be the same.

On Feb. 26, 1943, the patient became much worse. The skin and sclerae became a dusky yellow as well as cyanotic; the cyanosis was more pronounced on the paralyzed side (left). The skin was cold and dry, and numerous petechiae appeared above the umbilicus and in

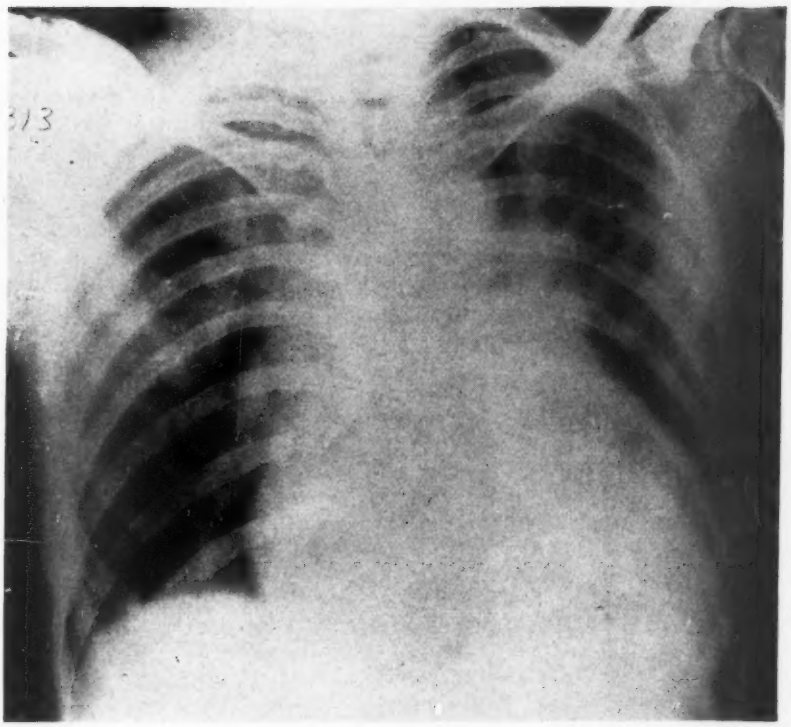


Fig. 3.—Roentgenogram of chest taken Feb. 24, 1943, showing little change from that of Aug. 28, 1943, except for slight increase in size. The prominence of the right border is still present.

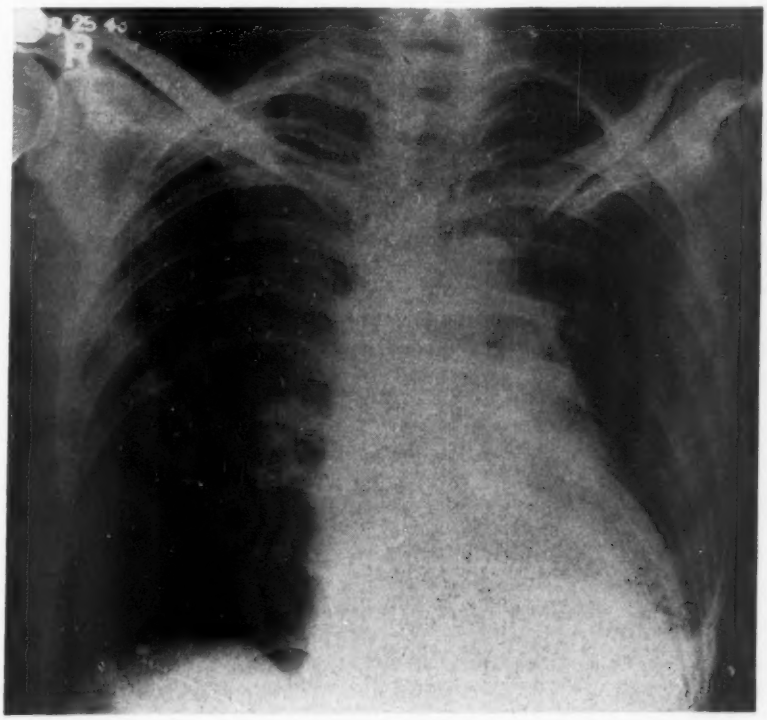


Fig. 4.—Roentgenogram of chest taken February 25, 1943 (twenty-four hours later). Note the marked reduction in the total size of the heart shadow, and especially the disappearance of the right auricular shadow behind the sterum.

scattered areas down the right leg. No difference in the peripheral pulsations on the right and left sides could be detected. The blood pressure was approximately 170/40-45, i.e., there was a marked increase in pulse pressure. The pulse was totally irregular and feeble, and the ventricular rate averaged 150. An electrocardiogram taken at this time is shown in Fig. 2*C*. Râles and rhonchi were heard throughout the chest. The abdomen was scaphoid without rigidity. Neither the liver nor spleen was palpable. The cervical veins showed no abnormal pulsations. The left-sided hemiplegia remained flaccid, but clonus involving the right arm and foot developed. A urea frost was noted over the face and trunk.

The nonprotein nitrogen rose at that time to 300 mg. per cent, with a creatinine of 5 mg. per cent; the blood sugar was 220 mg. per cent, and the chlorides, 672 mg. per cent. The blood cell count was essentially normal except for a terminal rise in the leucocytes to 50,000. Neither hematuria nor melena was noted at any time, although the observations were carefully checked. He died at 7:45 P.M.

Autopsy.—At autopsy the diagnoses were as follows: (1) Stenosis, mitral, severe. (2) Valvulitis, fibroblastic, aortic valve, ancient. (3) Endocarditis, verrucous, rheumatic; mitral valve and left auricle. (4) Thrombus, ball (diameter, 6.8 cm.), right auricle. (5) Thrombus, mural, left auricular appendage. (6) Hypertrophy and dilatation, right ventricle. (7) Dilatation, left and right auricles. (8) Pneumonia, confluent lobular, early. (9) Congestion, chronic, passive. lungs. (10) Emboli, thrombotic, mesenteric artery, secondary to mural thrombus, left auricle; old and recent. (11) Infarction, ileum, secondary to occlusion of mesenteric artery. (12) Peritonitis, generalized, secondary to infarction of intestine. (13) Infarction, spleen, moderately large, secondary to mural thrombus, left auricle. (14) Abscess, subdiaphragmatic, secondary to generalized peritonitis. (15) Abscess, spleen, at site of infarction, secondary to subdiaphragmatic abscess. (16) Encephalomalacia, right internal capsule, secondary to embolism arising from left auricle. (17) Hemorrhages, pontine. (18) Uremia (clinical). (19) Pericarditis, secondary to uremia, localized. (20) Frost, uremic, face and trunk. (21) Cirrhosis, cardiac type, moderately advanced. (22) Icterus, secondary to cardiac cirrhosis. (23) Proctitis, hemorrhagic, probably secondary to uremia. (24) Infarctions, left kidney, small, secondary to emboli arising from mural thrombus, left auricle.

Only the heart is described in detail. In situ the heart was moderately enlarged. Its greatest transverse diameter measured 15 cm. The shape was globular because of marked dilatation. The apex of the heart was located at the sixth rib. The epicardium near the pulmonary conus contained some fibrin; this was not conspicuous, however. The left auricle was markedly dilated, and had slightly displaced the esophagus to the right and exaggerated the tracheobronchial angle. A large, firm tumor could be palpated through the dilated right auricle. The coronary arteries were patent. They were of normal caliber and collapsed readily on section. Dissection of the heart revealed a large, smooth-surfaced yellowish mass in the right auricle. The mass was spherical and free to move, for it was not attached in any manner to the wall of the auricle. There was no evidence of a former pedicle. The diameter of the ball thrombus was 6.8 cm., and the circumference was 21.4 cm. The thrombus had considerably reduced the capacity of the auricle, and, in fact, it was difficult to see how much blood could have entered this chamber. Sections through the thrombus revealed

various hues of gray and red, with slight central softening. The endocardium of the right auricle and right ventricle was everywhere smooth any shiny. The tricuspid valve was markedly stretched, with a circumference of 14.5 cm. It was delicate and of tissue paper thinness. The papillary muscles of the right ventricle were thickened and somewhat shortened, and there was widening of the interpapillary spaces. The myocardium of the right ventricle measured 4 mm. in thickness. The left auricular appendage contained a dry, friable, inelastic mass of tissue which could be easily torn away except at its base. This mass of tissue measured 3 cm. in length. The free extremity of the mass was roughened, as if a portion had recently broken away. The anterior and posterior aspects of the wall of the left auricle were studded with small, reddish-pink, firm, globular, verrucous lesions. None of the verrucous lesions measured over 3 mm. in height. They were intimately adherent to the wall and could not be removed except at the expense of the endocardium. When removed, they left a raw surface. There were three plaques of these lesions. They covered an area of approximately 2 cm. each. The endocardium of the left ventricle was smooth and shiny. The pulmonary valve was delicate and of tissue paper thinness. The circumference of the mitral valve was, however, markedly reduced by fusion of the individual leaflets. The fusion of the leaflets prevented flattening out of the left ventricle when the valve was sectioned. The opening of the intact valve admitted only the tip of the index finger. It measured not over 1 cm. in diameter. The fused leaflets were markedly puckered and rigid. At the free margin the valve measured 4.5 mm. in thickness. A few millimeters from the valve margin there were numerous small, reddish-pink, verrucous lesions similar to those on the endocardium of the left auricle. Again, none of the lesions were friable, but they were moderately firm and difficult to remove. The chordae tendineae were noticeably shortened and appreciably thickened. The aortic leaflets were distinct, but were stiffened, and the margins were slightly puckered and thickened. The circumference of the valve was slightly reduced. No verrucous lesions were present on the aortic valve. The tricuspid valve was normal except for dilatation.

Microscopically, the right auricular tissue was normal. The tricuspid valve was likewise normal. The ball thrombus consisted of concentric layers of fibrin and platelets, with scattered erythrocytes and a few leucocytes. No Aschoff nodules were found in the myocardium of the right ventricle. Two pieces of the mitral valve were studied. The free margins of both were extensively thickened by connective tissue, much of which was hyalinized. At a slight distance from the end of the valve the superior surface was covered by fibrin masses that were attached to the valve by a single broad pedicle. Near the attached margins the underlying tissue was infiltrated by inflammatory cells consisting chiefly of lymphocytes, a few large mononuclears, and an occasional polymorphonuclear leucocyte. Throughout the area of infiltration by inflammatory cells there were scattered vascular spaces, some of which had relatively thick walls. The distal extremity of the aortic valve was thickened by hyalinized connective tissue. Only a few clusters of lymphocytes were seen near the outer margin. The sections of the left auricle showed that a portion of the endocardium was considerably thickened by connective tissue. On the outer surface of the thickened endocardium there was an irregular layer of fibrin, in the interstices of which were lymphocytes, large mononuclears, and a few plasma cells. This irregular layer corresponded to the vegetations described grossly.

In the epicardium of one section there was a zone of hemorrhage. In the myocardium subjacent to the vegetations, many of the fibers were separated for slightly greater distances than normal by connective tissue. No Aschoff nodules were noted. Two sections of the left auricular appendage were studied microscopically. Both contained a portion of the mural thrombus described grossly.

COMMENT AND SUMMARY

A case of ball thrombus in the right auricle of the heart is presented for the following reasons: (a) It is the first reported case of unquestionable ball thrombus in the right auricle; (b) it satisfies all of the criteria laid down by Welch for a true ball thrombus; (c) it produced a syndrome which, if encountered again, seems sufficiently characteristic to warrant consideration of a diagnosis of a thrombus acting as a ball valve mechanism over the tricuspid valve; (d) this possibility was suggested in the present case before death (it is not believed possible to ascertain before death whether or not the clot is attached by a pedicle); (e) this ball thrombus was of unusual size, i.e., 6.8 cm. in diameter; those previously reported varied from 1 to 4 cm. in diameter.

The syndrome which should lead to a consideration of ball thrombus (or other freely movable thrombus) in the right auricle includes the following: (1) Dusky cyanosis of the face and neck; (2) engorgement of the veins of the neck, with a systolic pulsation. This is even more significant if other veins, such as those of the arms and legs, show engorgement or a systolic pulsation; (3) marked dyspnea of oxygen hunger type, without adequate explanation in the form of difficulty in respiratory movement, obstruction, or congestion of the respiratory passages or lungs; (4) marked enlargement of the right side of the heart, especially the right auricle; (5) the presence of old rheumatic heart disease (almost universal); (6) auricular fibrillation; (7) mitral stenosis (not believed essential); (8) the presence of a murmur which could be established definitely as one of tricuspid insufficiency—or, even better—stenosis. (The present authors suspected tricuspid stenosis, but were never quite sure, and hesitated to make this rare diagnosis.) (9) marked engorgement of the liver, with a systolic pulsation; (10) a series of striking variations of this syndrome from extreme severity to relatively normal conditions, and vice versa, within short periods of time (six to forty-eight hours). This is the most important differential point between the possibility of a loose, riding thrombus and permanent organic changes in the tricuspid valve. Particularly noteworthy was the marked change in the roentgenograms of the heart within twenty-four hours, which occurred Feb. 24 to 25, 1943. It emphasized the importance of making serial roentgenograms during the fluctuating clinical phases whenever this syndrome is suspected.

Studies of particular interest which were not carried out in this case would be serial, carefully controlled, direct venous, and, if possible, direct arterial, pressure studies, and opaque medium studies of the

chambers of the heart. The effect, if any, of slow and sudden changes of posture would have been of interest.

Several pathologic changes are worthy of further comment. In this heart, as in most instances of ball thrombi in the left auricle, the mitral valve showed definite evidence of stenosis. It has been felt that stenosis encourages the formation and retention of ball thrombi. In this case, however, although the thrombus was in the right auricle, there was no evidence of tricuspid stenosis—rather, the tricuspid valve was markedly dilated—although this was considered to be secondary to the pressure of the thrombus in its endeavor to pass through. It was difficult indeed to understand how sufficient blood to maintain life could pass around the enormous ball and through the valve.

The history and the roentgenograms of August, 1942, suggest that this thrombus had probably been present for a period of six months or longer.

Characteristically, auricular fibrillation was present. This favors the development of mural thrombi and probably their detachment. The incomplete emptying and tendency to a rotary motion of the blood no doubt help to keep the thrombus from lodging permanently in the orifice. These same factors tend to develop the spherical shape by molding and grinding the surface as new accretions are added.

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Abstracts and Reviews

Selected Abstracts

Remington, J. W., Cartland, G. F., Drill, V. A., and Swingle, W. W.: Purification and Bioassay of Tissue Extracts Capable of Lowering the Blood Pressure of Hypertensive Rats. Am. J. Physiol. **140**: 627, 1944.

The protein material contained in various hog tissues which will lower the blood pressure of the hypertensive rat has been partially purified by ammonium sulfate and acetone fractionation steps. The evidence seems to suggest that this material is contained solely in the albumin fraction. Horse serum was found to be an exceptionally rich source of the active protein.

A rat assay method for the testing of this active material has been constructed, based on the blood pressure reduction obtained in hypertensive rats after intramuscular injections of the test material over a four day period. It has not been found possible to maintain the blood pressure below the hypertensive level for longer than ten to twenty days, even though extract injections were given continuously.

The reduction in blood pressure does not appear to be due to a general reaction to a foreign protein. Neither, however, can it be attributed to a single chemical entity contained solely in the kidney.

AUTHORS.

Wiggers, H. C., and Middleton, S.: Cardiac Output and Total Peripheral Resistance in Posthemorrhagic Hypotension and Shock. Am. J. Physiol. **140**: 677, 1944.

Utilizing a "modified Stewart Method" for determining cardiac output, variations of the latter and of total peripheral resistance (TPR) were studied during the course of standardized hemorrhagic shock in relation to other cardiodynamic events and hematocrit changes.

During a ninety minute period at 50 mm. Hg hypotension, and a subsequent forty-five minute period at 30 mm Hg, cardiac output and stroke volume were reduced to 29 to 45 per cent of the control flow. Although they were restored to normal in the majority of experiments immediately after reinfusion, in some the recovery was only to 45 to 85 per cent of control values. During the three hours succeeding reinfusion, cardiac output decreased rapidly and was the chief cause of the declining arterial blood pressure. In the final stages, cardiac output stabilized at low levels, and the continued fall of blood pressure was occasioned chiefly by peripheral factors. Slowing and failure of the heart were often the ultimate steps in the series of cardiodynamic events leading to death.

Hematocrit readings indicated a hemodilution during the periods of hypotension and a tendency toward concentration following reinfusion of the blood.

The course of events in standardized hemorrhagic shock is, therefore, similar to that described in other experimental types in that (a) hemoconcentration occurs, and (b) progressive reduction of cardiac output is chiefly responsible for the progressive decline of arterial pressures after reinfusion.

Despite the universally fatal outcome, changes in the total peripheral resistance were extremely variable during the periods of posthemorrhagic hypotension and during circulatory failure, which developed after reinfusion of blood. The different trends are analyzed. Arguments are advanced that physical factors concerned in such changes can be evaluated, and that an estimate of directional changes in vasomotor tone can be made. Supplementary evidence is cited from which the conclusion is reached that humoral or metabolic factors play a considerable role in these changes.

In the method for producing shock by holding mean arterial pressures at successive levels of 50 and 30 mm. Hg for specified intervals of time, cardiac output was reduced to 29 to 45 per cent of the original blood flow. Such ranges of reduction indicate that the procedure recommended for the rather regular production of hemorrhagic shock does not result in equivalent reductions of circulatory values when applied to different animals. Of course, the possibility that other factors may enter cannot be excluded.

AUTHORS.

Hamilton, W. F., Woodbury, R. A., and Harper, H. T., Jr.: Arterial, Cerebrospinal, and Venous Pressures in Man During Cough and Strain. Am. J. Physiol. **141:** 42, 1944.

Differential pressure records, which separate the changes in arterial pressure which are due to simple propagation of intrathoracic pressure from those which are due to changes in blood flow, are shown. It is shown that increases due to the first of the above causes, strain only the peripheral arteries, whereas increases due to changes in blood flow or to changes in peripheral resistance, strain also the vital arteries to the brain, spinal cord, and viscera.

The nature of the cerebrospinal pressure pulsations is discussed.

During the preliminary pressure rise of the cough, people whose circulation is hypodynamic show arterial pressures which are no higher than simultaneous intrathoracic pressures. During brief intervals there is, therefore, no effective head of pressure to irrigate the coronary or other vital vascular beds.

During the expulsive phase of the cough, the arterial pressure may continue to rise while the intrathoracic pressure is going down, or the arterial pressure may descend more slowly than the intrathoracic pressure. This signifies that the pressure distending the aorta is rising and, since it often occurs during diastole, it implies that during the expulsive phase of a cough blood is forced from the lungs through the relaxed left heart and into the aorta.

The cough may force blood into the aorta in cases with hypodynamic circulation and in cases with congestive heart failure. This may occur in normal individuals but no evidence has been obtained to support the idea that it does.

AUTHORS.

Stead, E. A., Jr., and Warren, J. V.: The Effect of the Injection of Histamine Into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand. J. Clin. Investigation **23:** 279, 1944.

Histamine injected intra-arterially increases the permeability of the capillaries supplied by the artery. The rapid loss of protein from the plasma can be detected by comparing the blood draining from the part before and after the injection. The hematocrit reading and hemoglobin concentration increased markedly while the protein concentration rose only slightly.

A reaction similar to that produced by histamine is not seen in uninjured tissue in the usual types of shock.

AUTHORS.

Bailey, C. C., and Betts, R. H.: Cardiac Arrhythmias Following Pneumonectomy. New England J. Med. **229**: 356, 1943.

Functional cardiac arrhythmias, especially auricular fibrillation and auricular flutter, occurred in eight of 78 patients who received total pneumonectomy but had no evidence of heart disease. In the authors' opinion, these arrhythmias alone do not indicate heart disease.

It seems best to restore the heart to normal rhythm as soon as practicable, either by rapid digitalization or, in selected cases, by quinidine sulfate, since heart failure may result if an excessively rapid cardiac rate continues over many days.

The etiology of these arrhythmias is unknown. The hypothesis is suggested that the precipitating factor is vagal irritation from a stitch abscess or infection of the bronchial stump, in the presence of hyperexcitability of the auricular muscle resulting from marked displacement of the mediastinum.

AUTHORS.

Currens, J. H., White, P. D., and Churchill, E. D.: Cardiac Arrhythmias Following Thoracic Surgery. New England J. Med. **229**: 360, 1943.

Cardiac arrhythmia is occasionally noted following thoracic surgery. Twelve patients are reported from a series of 56 who underwent surgery for carcinoma of the lung or esophagus. Eight had auricular fibrillation, and four auricular flutter.

Age seems to be a predisposing factor, since arrhythmia of the heart seldom occurs following thoracic surgery below the age of 40 years.

Quinidine sulfate may be used to advantage in such patients as a prophylactic measure during the postoperative period.

AUTHORS.

Mayer, C. P., Lepera, L., and Pataro, F. A.: Character of the Precordial Ventricular Complex in ECG Tracings With Deviation of the Electric Axis to the Left. Rev. argent. de cardiol. **10**: 223, 1943.

The precordial leads have a definite pattern in cases of left ventricular strain. In other types of left axis deviation, they do not differ from the normal controls. Therefore, the precordial leads are of value in the differential diagnosis between left ventricular strain and other types of left axis deviations. In the latter cases, when the precordial leads differ significantly from the normal, a coronary disease may be suspected.

AUTHORS.

Yuskis, A. S.: Aneurysm of the Right Pulmonary Artery With Rupture Into Bronchus, and a Patent Ductus Arteriosus; Report of a Case. California & West. Med. **58**: 272, 1943.

A congenital aneurysm confined to the right branch of the pulmonary artery, with rupture into the bronchus and a patent ductus arteriosus, is reported. An ante-mortem diagnosis, which was confirmed at autopsy, was made by the x-ray department of the State University of Iowa. This case report makes a total of thirty-one cases diagnosed ante mortem, and a total of 144 cases reported to the present time. The patient had relatively few symptoms and signs. There was no elevation of blood pressure, no prominence of the left side of the chest, no right-sided cardiac hypertrophy, and no electrocardiographic changes. The roentgen ray was unquestionably of chief assistance in establishing the diagnosis. The occurrence of these aneurysms is rare, but it is important to emphasize their consideration in the differential diagnosis of hemoptysis.

AUTHOR.

Hurst, A., Bassin, S., and Levine, I.: Miliary Densities Associated With Mitral Stenosis. Am. Rev. Tuberc. **49**: 276, 1944.

Chest x-ray surveys for tuberculosis are productive of a great deal of information on nontuberculous conditions.

Several cases of bilateral, symmetrical, diffuse, nodular, pulmonary densities associated with rheumatic mitral stenosis were discovered in draftees.

These miliary densities must be carefully distinguished from similar appearing conditions, such as miliary tuberculosis, sarcoidosis, pneumonoconiosis, carcinomatosis, etc.

An explanation for the varying roentgenographic appearance has been offered in the light of the probable pathologic and physiologic background.

AUTHORS.

Wedum, A. G., and Wedum, B. G.: Rheumatic Infections in Cincinnati Hospitals. Am. J. Dis. Child. **67**: 182, 1944.

There was a total of 3,475 admissions of patients with rheumatic infections to all hospitals in Cincinnati for the period from Jan. 1, 1930 to Dec. 31, 1940. Analysis of the records of these admissions and comparison with similar data obtained in Philadelphia for the period from 1930 through 1934 revealed the following facts:

The rheumatic syndrome was more nearly the same in Negroes in the two cities than it was in white persons. Negroes constituted a considerably greater proportion of the patients with rheumatic heart disease with rheumatic fever, and a somewhat smaller proportion of those with chorea than would be expected from their proportion in the population and in patients admitted to hospitals. Chorea is more common in Negroes than is generally realized.

In white persons in Cincinnati the incidence of rheumatic fever was lower, and the acute manifestations were less frequent, than in Philadelphia, and both morbidity and case mortality among children were lower. Among adults above the age of 35 years, the annual incidence of rheumatic heart disease per hundred thousand of population was greater in Cincinnati; this group accounted for more of the patients who died in Cincinnati than in Philadelphia. Adequate convalescent care for white children, and comparatively inadequate length of hospitalization for adults in Cincinnati, provide a possible explanation for these differences.

The data accumulated in this survey tend to corroborate the growing conviction that convalescent care, of proved value for children with rheumatic fever, should be given also to young adults. This concept is of major importance in handling rheumatic infections among young persons in military service.

AUTHORS.

Kuttner, A. G., and Krumwiede, E.: Observations on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks. J. Clin. Investigation **23**: 139, 1944.

Major and minor outbreaks as well as sporadic cases of streptococcal pharyngitis occurring in groups of rheumatic children in a sanatorium during a six-year period are described.

Major outbreaks were due to Group A streptococci of a single type not previously present, and were not preceded by a rise in carrier rate.

Minor outbreaks were preceded by a slow spread from carriers to other individuals without at first causing infection. Subsequently, a small number of clinical cases due to these types developed.

Sporadic cases arose directly from carriers and were not preceded by a dissemination of the streptococci to healthy individuals.

The length of the carrier state was studied.

Twenty-nine per cent of the children admitted during the summer and fall months were carriers of Group A hemolytic streptococci. With few exceptions, these microorganisms did not spread to other individuals and disappeared after a few months.

The epidemic-inducing types of streptococci persisted longer in "post-infection" than in "contact" carriers.

The length of the carrier state was not related to the presence or absence of tonsils.

AUTHORS.

Kuttner, A. G., and Lenert, T. F.: The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery From Streptococcal Pharyngitis. J. Clin. Investigation **23**: 151, 1944.

The development of bacteriostatic properties in the blood of children, after recovery from upper respiratory infections due to Group A streptococci of a single type, is reported.

AUTHORS.

Higgins, G. K.: The Effect of Pulmonary Tuberculosis Upon the Weight of the Heart. Am. Rev. Tubere. **49**: 255, 1944.

The total heart weights of 600 carefully selected patients dying from pulmonary tuberculosis have been tabulated by age, body length, and estimated body weight. These have been compared with normal heart weights selected from the literature.

Right ventricular weights above Müller's averages were found in 23 per cent of the tuberculous patients and a ventricular ratio (L/R) of less than 1.3 was present in 40 per cent. The right ventricle weighed more than the corresponding left in 15 per cent of the tuberculous patients.

It was not possible to determine a definite relationship between right ventricular hypertrophy and pleural adhesions, pulmonary collapse, or the type and extent of the pulmonary tuberculosis.

A definite relationship existed between right ventricular hypertrophy and the clinical duration of the disease.

Left ventricular hypertrophy was not noted in this series.

A theory has been presented to explain the presence of right ventricular hypertrophy in some patients and its absence in others with similar tuberculous lesions.

AUTHOR.

Gordan, G., Soley, M. H., and Chamberlain, F. L.: Electrocardiographic Features Associated With Hyperthyroidism. Arch. Int. Med. **73**: 148, 1944.

In this series of cases of hyperthyroidism the noteworthy electrocardiographic findings in order of frequency were: (1) sinus tachycardia, (2) various abnormalities of the T waves, of which low amplitude and notching were the most common, (3) auricular fibrillation, (4) partial auriculoventricular block, and (5) in rare instances, auricular flutter. After exclusion of other causes for electrocardiographic abnormalities, the incidence of these findings was the same for the younger (14 to 40 years of age) and for the older (41 to 75 years of age) groups of patients. After treatment of hyperthyroidism, the abnormalities tend to disappear. In the presence of hyperthyroidism, electrocardiograms must be interpreted with caution, since they may simulate those of persons with organic heart disease.

AUTHORS.

Middleton, S., and Wiggers, C. J.: The Effects of Renin and Angiotonin on Cardiac Output and Total Peripheral Resistance. Am. J. Physiol. **141**: 128, 1944.

The effect of renin and angiotonin on cardiac output was studied by a refined quantitative cardiometer method.

Small doses cause insignificant changes in systolic discharge in the direction of slight increases or decreases, but the concomitant slowing reduces cardiac output per minute slightly. A study of changes in total peripheral resistance indicates that the pressor rise offers a reasonable indication of the magnitude of peripheral vasoconstriction.

More potent doses, generally those which cause a pressor effect of 30 mm. Hg or more, result in a variable reduction in systolic discharge and, together with cardiac slowing, may reduce cardiac output per minute very significantly. In such instances, pressor effects underestimate the change in total peripheral resistance considerably.

Since such cardiac depression may persist after use of larger doses, the return of arterial pressure to control levels may not be a sign that its peripheral action has passed off. In all tests requiring repeated injections, it is recommended that doses be used which do not evoke pressor effects in excess of 30 mm. Hg.

AUTHORS.

Middleton, S.: The Effects of Renin and Angiotonin During Hemorrhagic Hypotension and Shock. Am. J. Physiol. **141**: 132, 1944.

The effects of renin and angiotonin in doses causing a pressor response of 30 mm. Hg, or less, were determined during two stages of posthemorrhagic hypotension and at various periods after reinfusion of the blood, i.e., during development of precipitate or delayed circulatory failure regarded as characteristic of shock.

In confirmation of other investigators, it was found that the pressor responses to *both* of these agents diminished and then disappeared during the prolonged hypotension, but recovered and increased progressively after reinfusion of the blood, despite the development of circulatory failure.

The results failed to support the suggestion that the mechanisms by which renin is activated are implicated in the development of circulatory failure, and that the gradual return of response during progressive circulatory failure after reinfusion remains unexplained.

AUTHOR.

Jonnard, R., and Thompson, M. R.: The Nature of the Pressor and Depressor Factors Derived From the Kidney. J. Am. Pharm. A. **32**: 260, 1943.

Various hypotensive kidney extracts have been fractionated and the acute effects upon the carotid and femoral arterial blood pressure, pulse rate, abdominal vasomotor system, respiration, and electrocardiogram have been studied in anesthetized and nonanesthetized dogs and cats. The substance or substances which are responsible for the production of prolonged hypotension in normal animals are characterized by their solubility in water, strong alcohol, concentrated acetone, dichloroethylene, by the presence of phenolic hydroxyls of a tryptophan group, by the absence of free histidine, or reducing properties, or sterols, lipids, and phospholipids groups, by their destructive oxidation by vegetable phenolase, by their slow mobility in the electrophoretic field, by their isoelectric point between pH 5.0 and 7.0, and by their incapacity to traverse ultrafilters. These facts indicate the presence of complex molecules which are responsible for the slow resorption rate. This, in turn, explains the prolonged hypotension produced when these substances are injected sub-

cutaneously or intramuscularly. The pharmacologic properties of the kidney hypotensive extracts described and their effects upon the arterial blood pressure and the action current of the heart are apparently not specific of the substances considered when compared with records obtained in human cases of essential hypertension. The destructive oxidation of renin and of the hypotensive kidney extracts by vegetable phenolase (tyrosinase) has been studied. It has been demonstrated that, while renin yields upon oxidation an unstable strongly hypotensive substance, the oxidation of the hypotensive kidney extracts yields an inactive preparation, and that the two reactions proceed independently in mixtures containing both factors, so that there is no in vitro chemical antagonism or reciprocal neutralization between renin and the kidney hypotensive fractions isolated. The possible role of these substances and of renin in the pathogenesis of hypertension of renal origin has been discussed in the light of a number of clinical facts reported to date. It is advanced that possibly the role of the kidney derangement is more of a metabolic nature than of a humoral one. On the other hand, results of the oxidation experiments reported suggest a new therapeutic approach worth further investigation.

JONNARD.

Greenfield, I.: Thrombosis and Embolism of the Abdominal Aorta. Ann. Int. Med. **19**: 656, 1943.

A case of embolism of the abdominal aorta is reported.

The association of miliary tuberculosis, peritonitis, urinary sepsis, and yellow atrophy of the liver with thrombosis of the abdominal aorta was noted.

Variations from the classical clinical syndrome of occlusion of the abdominal aorta were cited.

Five additional cases of occlusion of the abdominal aorta were added, making the total number of cases now on record 161.

AUTHOR.

Watson, J. R., Lichty, J. M., Hill, J. M., and Miller, R. B.: The Use of Venograms for the Localization and Study of Arteriovenous Fistula. Surg., Gynec. & Obst. **76**: 659, 1943.

Three cases of arteriovenous fistula of the common femoral vessels are reported in which venography was proved to be a reliable means of locating the level of the fistula.

Studies of the venograms in each instance showed the vein distal to the fistula to be normal.

The venograms demonstrated a marked difference in the collateral venous circulation between one case in which the vein had been ligated distal to the fistula at the time of injury for control of hemorrhage, and two cases in which this had not been necessary.

Ligation of the vein distal to the fistula appears to have the same beneficial effect on the extremity that ligation proximal to the fistula has on the heart.

AUTHORS.

Reich, N. E.: Occlusions of the Abdominal Aorta: A Study of 16 Cases of Saddle Embolus and Thrombosis. Ann. Int. Med. **19**: 36, 1943.

Occlusion of the abdominal aorta should be strongly suspected when there is a sudden onset of pain of varying intensity in the lower extremities and pelvis with temperature and color changes, sensory disturbances, and weakness or paralysis. This possibility becomes greater when occurring in females with auricular fibrillation due to rheumatic heart disease, especially when signs of embolization have occurred in other organs. An early diagnosis may result in cure or arrest by surgical

intervention (embolectomy), heparinization, or other appropriate medical measures described herein.

AUTHOR.

Doane, J. C.: Embolism and Thrombosis of the Popliteal Artery—Diagnosis and Treatment. Ann. Int. Med. **19**: 634, 1943.

Eleven cases of popliteal occlusion were presented. Comments on the symptoms as related to diagnosis were made. The necessity of early diagnosis was stressed, it being stated that treatment, whether it be radical or conservative, must be begun within the first six hours if good results are to be expected.

The value of a carefully planned conservative routine was pointed out. The technique of heparinization was briefly described.

AUTHOR.

Chamberlain, E. N.: Bacterial Aneurysm. Brit. Heart J. **5**: 121, 1943.

Three new cases of bacterial aneurysm are described: one of the femoral artery, one probably of the radial artery, and one of the mesenteric artery. The last ruptured, causing death from hemorrhage into the peritoneal sac. The post-mortem findings are recorded in two cases.

Nineteen other cases have been collected, reported since 1923 when the subject was fully dealt with by Stengel and Wolferth. These have been analyzed.

AUTHOR.

Hamilton, W. F.: The Patterns of the Arterial Pressure Pulse. Am. J. Physiol. **141**: 235, 1944.

The pressure pulse patterns in various arteries are described in terms of the filling and emptying of the arterial tree and the added reflected waves which are contributed by the various arteries. It is shown that these waves are reflected from constricted arterioles, and that the form of the pulse may be used to evaluate the role of vasodilation in producing hypotension.

AUTHOR.

Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure: An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients With Prolonged Congestive Failure. Arch. Int. Med. **73**: 138, 1944.

Edema develops in chronic congestive failure because the kidneys do not excrete salt and water in a normal manner. This disturbance in renal function is related to the decreased cardiac output, and not to engorgement of the kidneys from an increased venous pressure, because the salt and water retention may occur before there is a rise in venous pressure.

The increase in the plasma volume is a manifestation of the retention of salt and water. The resulting decrease in concentration of the plasma proteins usually stimulates production of plasma protein so that the total amount of circulating protein increases. The plasma volume is thus increased in size without a marked lowering of the osmotic pressure of the plasma proteins.

In due time, the increase in the blood volume and the extracellular fluid volume causes a rise in the venous pressure. The osmotic pressure of the plasma proteins and the increased pressure of the extracellular fluid provide the physical forces which enable the large plasma volume to be maintained in the presence of the high capillary pressure which results from the high venous pressure.

Local differences in venous pressure are of importance in that they determine the placement of the salt and water which are retained by the kidneys in congestive heart failure.

Other factors than retention of salt by the kidneys account for the rise in venous pressure in acute heart failure. In many patients the rise in venous pressure represents the summation of the effects of acute and chronic heart failure.

AUTHORS.

Rinzler, S. H., Travell, J., and Civin, H.: The Oscillometric Index: An Aid in Evaluating the Arterial Status of the Lower Extremities. Arch. Int. Med. **73:** 241, 1944.

The oscillometric index (ratio of the oscillometric reading at the ankle to that at the wrist), the cutaneous temperature following posterior tibial nerve block, and the presence or absence of calcification of the vessels of the lower extremities in the roentgenogram were determined for eighty-four ambulatory patients with heart disease.

A correlation of the data obtained by these three laboratory aids (oscillometry, cutaneous temperature test, and soft tissue roentgenogram) shows that, as the oscillometric index decreases, the incidence and extent of calcification of the vessels of the lower extremity, and the incidence of abnormal cutaneous temperatures increase.

In the presence of a normal circulation in the upper extremity, an oscillometric index of 0.75 or more almost always indicates adequate arterial function in the lower extremity. Similarly, an index of less than 0.75 indicates sclerotic changes in the arteries of the leg, probably with calcification, and an index of 0.3 or less indicates extensive calcification and probably advanced occlusive arterial disease.

The oscillometric index is of greater value in estimating the presence and degree of arteriosclerotic disease in the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within an intermediate range of about 1 to 4 at the ankle and ⅛ to 2 at the foot.

An oscillometric reading of 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow, and a reading of less than 1 at the ankle or 0 at the foot indicates occlusive arterial disease.

Roentgen examination for calcification of the vessels usually affords the earliest evidence of arteriosclerosis of the lower extremities.

Final appraisal as to the degree of occlusive arterial disease of the lower extremities ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature.

Duplicate determinations of cutaneous temperature on ten patients showed that a variation of several degrees (C.) in the room temperature does not materially influence the vasodilatation temperature after posterior tibial nerve block.

AUTHORS.

Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment by Intra-Arterial and Intravenous Infusion of Blood. Arch. Surg. **47:** 178, 1943.

A method for producing hemorrhagic shock is described which produces severe sustained hypotension without increase of bacterial contamination or the use of excessive amounts of anticoagulants. Spontaneous recovery does not occur. An apparatus is described for return of the blood removed through an artery under controlled pressure.

The severity of the effects of the hypotension on the vascular system was ascertained by the pressor response to angiotonin or epinephrine. If the response is not restored after treatment the chance of survival is poor, but the return of responsiveness does not insure survival.

When all the blood removed is returned by the intra-arterial route under a pressure of 50 mm. of mercury the systemic arterial pressure rises rapidly and recovery

occurs. The same amount of blood given intravenously usually causes recovery, but not quite so certainly as blood given into an artery.

Readministration of only 50 per cent of the blood by vein resulted in recovery of 30 per cent of the dogs, while the same amount given intra-arterially resulted in recovery of 75 per cent.

When blood is given intra-arterially to animals with severe hypotension two precautions should be observed: First, the pressure should not be greater than 50 mm. of mercury, and it should be elevated stepwise. Second, the rate of administration of the fusion should be guided by the venous pressure.

Intra-arterial infusions have been given three patients in severe shock to demonstrate the practicality of the procedure.

It is suggested that the method may have value when the amount of plasma or blood available is insufficient or when the arterial pressure is excessively low.

AUTHORS.

Rich, Arnold R.: A Peculiar Type of Adrenal Cortical Damage Associated With Acute Infections, and Its Possible Relation to Circulatory Collapse. Bull. Johns Hopkins Hosp. **74**: 1, 1944.

Various acute infections produce damage to the adrenal cortex, leading to necrosis of isolated cells, and to a striking transformation of the solid cords of the zona fasciculata into tubular structures containing an inflammatory exudate.

The possible relation of this adrenal cortical damage to the circulatory collapse that occurs in some of the patients who suffer from these infections, is suggested.

AUTHOR.

Cole, W. H., Allison, J. B., Murray, T. J., Boyden, A. A., Anderson, J. A., and Leathem, J. H.: Composition of the Blood of Rabbits in Gravity Shock. Am. J. Physiol. **141**: 165, 1944.

Rabbits suspended head up, without anesthesia, became unconscious in from twenty to one hundred and twenty minutes, even though breathing continued at a rate about one half that of normal. Thirty per cent of the animals died within twenty-four hours although all external symptoms appeared normal.

Other changes resulting from suspension were: (a) marked reduction of blood pressure, (b) suppression of urine flow, (c) metabolic acidosis (pH = 7), (d) decreased blood carbon dioxide and venous oxygen, (e) increased plasma lactate, phosphate, pyruvate, potassium, and nonprotein nitrogen, (f) increased or decreased plasma glucose, and (g) decreased plasma chloride in well-fed animals.

There were no constant or significant changes in hematocrit, plasma specific gravity, protein, sodium, or calcium, or in the blood cell counts.

Hemoconcentration did not occur.

Suspension resulted in a peripheral circulatory deficiency leading to tissue hypoxia. Altered concentrations of certain blood metabolites occurred, which were useful in determining the severity of shock, and the course of recovery, when the rabbits were returned to the horizontal position.

AUTHORS.

Houchin, O. B., and Smith, P. W.: Cardiac Insufficiency in the Vitamin E Deficient Rabbit. Am. J. Physiol. **141**: 242, 1944.

We have shown that rabbits in a state of nutritional muscular dystrophy as the result of Vitamin E deprivation exhibit the following signs of severe myocardial damage:

A greatly increased sensitivity to posterior pituitary extracts; they are killed by doses much smaller than those which are well tolerated by normal control animals.

A high resistance to the toxic effects of the cardiac glycosides; their lives are preserved for several days beyond the predicted time of death in the majority of cases, by doses of digoxin or ouabain which are lethal to normals.

Probable cardiac dilatation, as revealed by thoracic x-ray films.

From these findings we conclude that the sudden death of Vitamin E deficient animals in an advanced stage of muscular dystrophy is due directly to myocardial failure.

AUTHORS.

Mayerson, H. S.: Orthostatic Circulatory Failure (''Gravity Shock'') in the Dog. Am. J. Physiol. 141: 277, 1944.

Anesthetized dogs, suspended in the upright (feet down) position for twenty minutes to four hours, show varying degrees of hypotension, progressive hemoconcentration, and marked increases in arterio-venous oxygen and carbon dioxide differences. After ten to twenty minutes, the plasma protein level diminishes, while the protein concentration of lymph increases. These changes can be reversed by returning the animals to the horizontal position and approximately controlled values are achieved in about thirty minutes.

Animals kept in the upright position are extremely sensitive to hemorrhage. Irreversible failure is often precipitated by the withdrawal of relatively small quantities of blood (30 to 50 c.c.). This can usually be prevented, and the response of tilting improved, by the infusion of saline and/or blood during the upright period.

AUTHOR.

Stead, E. A., Jr., and Warren, J. V.: The Protein Content of the Extracellular Fluid in Normal Subjects After Venous Congestion and in Patients With Cardiac Failure, Anoxemia, and Fever. J. Clin. Investigation 23: 283, 1944.

The filtrate from the capillaries of the skin and subcutaneous tissues normally contains some protein. On the average, it does not contain more than 0.24 gram per cent of protein. It probably contains much less.

Elevation of the venous pressure in the leg to a level equal to 30 mm. Hg. produces edema which contains from 0.4 to 1.3 grams per cent of protein, with an average of 0.8 grams per cent.

Cardiac failure does not make the capillaries of the leg more permeable to protein.

Generalized anoxemia, sufficient to cause impaired cerebral function, does not cause increased permeability of capillaries in the leg. Although local ischemia produces capillary damage and leakage of protein, generalized stagnant anoxia, of a degree compatible with life, does not make the capillaries of the leg more permeable to protein.

Fever and acute infectious disease cause no abnormal increase in permeability to protein in the capillaries of the leg.

AUTHORS.

Wilburne, M., and Ceccolini, E. M.: Heart Disease in Selective Service Examinees. A Study of 20,000 Examinees in the Pacific Northwest. Am. J. M. Sc. 207: 204, 1944.

A study of 20,000 consecutive Selective Service examinees, representing a cross-section of male population 20 to 45 years of age in the Pacific Northwest, revealed the existence of heart disease in 288 men, an incidence of 1.44 per cent. This figure constituted 6 per cent of rejections of all physical and mental defects.

Rheumatic heart disease was observed in 183 examinees, or 63.5 per cent of cardiac rejections and 9.15 men per 1,000 examined. Congenital heart disease

followed in frequency, occurring in 35 men (12.2 per cent of rejections for heart disease, or 1.75 men per 1,000 examined). There were nine instances of arteriosclerotic heart disease, six examinees with hypertensive heart disease, three cases each of hyperthyroid heart disease and effort syndrome (neurocirculatory asthenia), two instances of paroxysmal tachycardia, and one case of chronic constrictive pericarditis.

There were 46 cases of organic heart disease of unknown etiology, or 16 per cent of total cardiac rejections and 2.3 men per 1,000 examined.

In the 183 examinees rejected for rheumatic heart disease the mitral valve was involved alone in 152 cases (3.1 per cent), the aortic valve was involved alone in eight examinees (4.4 per cent), and combined mitral and aortic valve defects were observed in 23 cases (12.5 per cent).

Functional murmurs were noted in 297 examinees, an incidence of 1.48 per cent of the total number of men examined. This figure represents an incidence slightly higher than that observed for all forms of cardiac disease combined.

The figure of 288 men rejected for heart disease (1.44 per cent of 20,000 examinees) is of interest in comparison with 4,820 rejected for all physical and mental defects (24.1 per cent of examinees).

AUTHORS.

Plentl, A. A., and Page, I. H.: The Action of Crystalline Proteolytic Enzymes on Angiotonin. J. Exper. Med. **79**: 205, 1944.

Angiotonin was subjected to enzymatic digestion by crystalline carboxypeptidase, chymotrypsin, trypsin, and pepsin. These enzymes were found to destroy it in vitro. Hydrogen ion optima and proteolytic coefficients for these reactions were determined and were found to be of approximately the expected magnitude for typical substrates.

Regarding the purified crystalline enzymes as reagents, the experimental findings were interpreted on the basis of Bergmann's specificity studies. The authors were thus directed to the conclusion that angiotonin contains (1) a free terminal amino group, (2) a free terminal carboxyl group, (3) one basic amino acid residue which may be terminal but its carboxyl must be united in a peptide linkage, (4) one central dibasic amino acid residue in combination with an aromatic amino acid residue, (5) an aromatic amino acid residue which may be part of (4) and, if not part of (4) must be terminal with its carboxyl group in peptide linkage. The simplest compound satisfying these conditions is tyrosyl-arginyl-glutamyl-phenylalanine or a combination of amino acids with similar general characteristics.

AUTHORS.

Koffler, A., and Freireich, A. W.: Thrombophlebitis as a Hitherto Unreported Complication of Thiocyanate Therapy of Hypertension. Am. J. M. Sc. **207**: 374, 1944.

Four cases of thrombophlebitis (an incidence of 10 per cent) are reported as occurring in the course of therapy of hypertension with thiocyanate. This high frequency is much greater than can be explained on pure coincidence, and must be accepted as a toxic effect which has not been previously reported.

It does not appear to be related to the level of thiocyanate in the blood, and may occur early or late in the course of treatment.

AUTHORS.

Book Reviews

ESTUDO PATOLÓGICO DA AÇÃO DO TABACO DESNICOTINIZADO SÔBRE OS VASOS SANGUINEOS DO RATO BRANCO: By J. Lopes de Faria, Universidade de Minas Gerais. Grafica Queizoz Breiner Ltda., Belo Horizonte, Brazil, 1943, 107 pages, 56 illustrations.

Forty-one rats were injected with a denicotinized extract of tobacco which was prepared according to Harkavy's technique. Thirteen rats served as controls, and were injected with saline solution. In the latter parts of the experiments, which lasted 114 days, doses of 4 times as much and then 18 times as much of the extract as Harkavy used were injected. Chronic endocarditis, myocarditis, and pericarditis were noted on microscopic examination of both test animals and control animals. The author concludes that nicotine-free extracts of tobacco, specifically that grown in Minas Gerais, do not produce pathologic changes in the blood vessels of the hearts and extremities of white rats. He was thus unable to confirm the studies of Harkavy. This, he believes, may be due to the fact that the tobacco which he used had a lower "antigen power" than that employed by Harkavy.

EDGAR V. ALLEN.

SINDROME CORONARIO LATERAL: By Guillermo A. Bosco, Professor Titular de Semiologia y Clinica Propedeutica de la Facultad de Ciencias Médicas de Buenos Aires. Imprenta Ferrari Hnos., Buenos Aires, 1943, 168 pages, 83 illustrations.

As is made clear in the introduction, this monographic study strives to establish the "lateral coronary syndrome" as an anatomicoclinical entity to be considered together with the "anterior" and "posterior" coronary syndromes.

The syndrome is caused by occlusion of the left circumflex artery in its terminal portion. This artery is distributed over the lateral portion of the left ventricle in about 80 per cent of all persons, and over the posterior part of the septum and the right ventricle in the others. The author states that this possibly "anomalous" distribution need not be taken into account, for only the left ventricle might show the effects of acute ischemia; it is the reviewer's opinion that this is not valid.

The first part of the book is devoted to an anatomic and pathologic study, and is illustrated by exceptionally clear photographs. A physiopathologic study follows.

The clinical signs of the "lateral syndrome" are discussed in detail. In spite of the author's efforts, they do not seem to be essentially different from those caused by occlusion of other coronary arteries. The cardiac manifestations are sinus tachycardia, gallop rhythm, friction rub, functional mitral systolic murmur, and ventricular alternation. It is emphasized that attacks of either left ventricular premature beats or left ventricular tachycardia may occur.

The early electrocardiographic abnormalities are depression of the S-T segment in Leads I and IVF and elevation of the S-T segment in Lead III. Differentiation from posterior infarction may be difficult at times. The author agrees with Wood

and his co-workers, but not with Katz, who describes changes in the S-T segment in Leads I and III similar to those associated with posterior infarction, and changes in the precordial leads like those which occur with anterior infarction, i.e., a special electrocardiographic pattern.

No mention is made of the original description of the syndrome by Wood, Wolferth, and Bellet (AM. HEART J., **16**: 387, 1938), nor is there any historical approach or quotation from the literature.

In spite of the efforts of the author, a differentiation between this and other coronary syndromes does not always seem possible.

Wood and his co-workers emphasized the frequency of auricular fibrillation, but Bosco, on the other hand, stresses ventricular premature beats and ventricular tachycardia. This difference of opinion undoubtedly leaves a field for future investigation.

ALDO LUISADA.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

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American Heart Journal

For the Study of the Circulation

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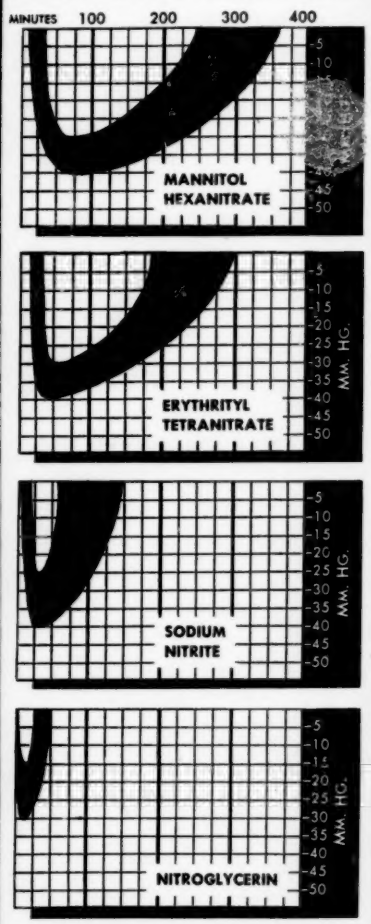

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